UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/404,706 | 09/23/1999 | LEWIS T. WILLIAMS | 2300-1492 | 8702 |

27476 7590 07/16/2003

Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

| EXAMINER |
|---|
| ZHOU, SHUBO |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1631 | |

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/404,706 | WILLIAMS ET AL. | |
| | Examiner | Art Unit | |
| | Shubo "Joe" Zhou | 1631 | |

*-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --*

**Peri d for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *3/22/01, 5/14/01, and 8/19/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disp sition of Claims**

4)☒ Claim(s) *13-102* is/are pending in the application.

4a) Of the above claim(s) *13-66 and 75-102* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,10* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *14,5* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other:
(1) Suggestion for Deposit of Biological Material
(2) Search Summaries for GenEmbl
(3) Revised Interrim Written Description Guidelines Training Materials.

# DETAILED ACTION

## *Election/Amendments*

Applicants' election, with traverse, of Group II (original claims 6,7,10, and 11, which are now canceled) in Paper No.8, filed 3/19/01, and the election of SEQ ID NO:635 in Paper No. 13, filed 5/14/01, are acknowledged. The traversal is on the ground(s) that up to ten sequences should be examined according to the MPEP 803.04. This is not found persuasive because, as cited by the applicant, the MPEP also indicates that the complex nature of the claimed material in some cases may necessitate that the reasonable number of sequences to be selected be less than ten. In the instant case, the claimed nucleic acids are considered complex in nature and thus less than ten sequences are to be elected. Further, it is noted that the multitude of sequence submissions for examination has resulted in an undue search burden if more than one nucleic acid sequence is elected, thus making the previous waiver for up to 10 elected nucleic acid sequences effectively impossible to reasonably implement.

The requirement is still deemed proper and is therefore made FINAL.

Applicants canceled the original claims 1-12 and presented new claims 13-102 in Paper No. 8, filed 3/19/01. In light of the election of Group II and SEQ ID NO:635, also as indicated by applicants in Paper #13, filed 5/14/01, only claims 67-74 are drawn to the elected invention and under consideration; claims 1-66, and 75-102 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Applicants' amendments filed in Paper No. 8 have been entered.

## *Sequence Rule Compliance*

Applicants' amendment filed 8/15/02 in response to the Office communication regarding sequence rules non-compliance, mailed 7/17/02, is acknowledged. The paper copy and the computer readable form of the Sequence Listing are received and entered without error.

However, it is noted that this application still contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a) (2), such as the sequences on page 49, and elsewhere of the specification, yet, this application fails to comply with the requirements of 37 CRF 1.821 through 1.825 because these sequences are not followed by a sequence identifier (SEQ ID NO:X) and not listed in the Sequence Listing. Applicants are reminded that it is required that SEQ ID Nos be amended into the specification at each sequence. If new sequences are added to the Sequence Listing, a new paper copy and computer readable form of the new Sequence Listing, as well as a new statement under 37 C.F.R. 1.821(f) are required. Failure to respond to this requirement may result in abandonment of the instant application.

## *Priority*

It is brought to applicants' attention that for the purpose of examination, the Office has not been able to determine that the elected SEQ ID NO:635 was disclosed in the provisional applications 60/102,161; 60/102,380; 60/103,815, and 60/105,877, to which applicants claimed priority. Prior art published after the claimed provisional applications but before the filing date of

the instant application may have been cited in this Office action. Applicants are requested to provide evidence that the elected invention is indeed disclosed in the prior applications if they wish to contest the citation of the intervening prior art.

## *Information Disclosure Statements*

The Information Disclosure Statements filed on 3/31/00, and 4/23/01 have been entered and considered. Initialed copies of the form PTO-1449 are enclosed with this action.

## *Biological Deposits*

It is noted that claim 72 is drawn to a polynucleotide comprising the nucleotide sequence of an insert contained in a clone deposited as clone number M00027169D:H06 of ATCC Deposit Number PTA-758. The conditions of deposit for the claimed clone are described in the specification on page 65. However, the conditions for deposit do not satisfy the requirements of 37 CFR 1.808 because the address of the depository ATCC is not given, and a statement has not been made that restrictions will be irrevocably removed upon granting of the patent. Further, the date of deposit is not clearly provided. On page 65, lines 11-12, the specification states that the clones including M00027169D:H06 of ATCC Deposit Number PTA-758 are deposited on or before 5/13/99, and yet on line 15, it states that the clones are deposited on or before 9/23/99. Clarification is requested. See MPEP §§ 2410 and 2410.01 and the attached suggestions for deposit of biological material. See also the rejection of claim 72 under 35 U.S.C. § 112 (enablement rejection) as set forth below.

## *Specification*

The disclosure is objected to because of the following informalities:

The specification on page 65 refers to "tables numbered 22 and greater (inserted before the claims)". However, there are no tables numbered 22 and greater to be found in the specification.

Appropriate correction is required.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

## *Claim Rejections-35 USC § 101/ § 112*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Claims 67-74 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility due to its not being supported by a specific, substantial, and credible utility or, in the alternative, a well-established utility.**

Claims 67-74 are drawn to nucleic acid molecules comprising the sequence of SEQ ID NO:635 or 15 contiguous nucleotides thereof, or nucleic acids 90% identical thereto, or nucleic acids that hybridizes thereto, or vector comprising the nucleic acid molecules and recombinant cell comprising such vector. The claimed nucleic acids are not supported by a specific asserted utility because none of the disclosed uses of the nucleic acids in the specification is specific. For example, the specification states that the polynucleotides can be used in mapping, tissue profiling, detection of expression level, etc. (see pages 23-43). These are not specific uses for the claimed nucleic acids because they are generic to any nucleic acids derived from an organism. Applicants list a number of possible uses but fail to assert a specific utility for the claimed nucleic acids. None of the utilities asserted is specifically linked to the claimed nucleic acids comprising the sequence of SEQ ID NO:635 or portions thereof. Further, the claimed nucleic acids are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. For example, the specification states that the nucleic acids can be used for diagnosis of human disease by monitoring the expression level of the nucleic acids (page 27). However, the specification does not provide specific diseases that can be diagnosed by monitoring the expression level of the claimed nucleic acids, nor does it provide whether hyper- or hypo-expression of the nucleic acids is associated with disease. Therefore, one of skill in the art would have to perform further research to determine what, if any, disease is specifically linked to the mis-regulation of the expression of the claimed nucleic acids, and what expression pattern of the claimed nucleic acids (e.g. hyper-expression or hypo-expression) is linked to the disease in order to find any practical usage for the nucleic acids. The apparent need for such

further research indicates that the claimed nucleic acids are not disclosed as to a currently available or substantial utility.

Further, neither the specification as filed nor any art of record discloses or suggests any property or activity for the claimed nucleic acid such that a non-asserted utility would be well established for the nucleic acids.

It is noted that Table 2A on page 120 of the specification appears to assert that SEQ ID NO:635 shares homology with a database sequence M13973, which appears to encode a bovine protein kinase C. It is not clear from the specification as to the percentage of homology, but the search results by the Office of the database GenEmbl with SEQ ID NO:635 as query show that the overall match of SEQ ID NO:635 with M13973 is only 25.3%. See result No.84 of the attached search "Summaries". One of skilled in the art, however, would have reasons to doubt that the claimed nucleic acids indeed encode a protein kinase C protein for the following reasons:

Firstly, it would have been well known in the art that sequence similarity does not reliably correlate to sequence similarity and that sequence similarity does not reliably result in similar or identical biological activities. For example, it would have been well known that even a single nucleotide or amino acid change or mutation is able to destroy the function of the biomolecule in many instances, albeit not in all cases. In the absence of factual evidence characterizing the structural and functional components of the biomolecule, the effects of these changes are largely unpredictable as to which ones will have a significant effect and which ones will be silent mutations having no effect. The prior art cannot *unambiguously* assign function to an unknown gene based on a homology comparison. The following example demonstrates that assignment of a metabolic gene to a known function based on homology comparisons alone

provide improper functional assignment (see the homology-based methods of functional assignment of Everett et al., Nature Genetics *17*, 411-422, **1997** in light of the experimental conclusions of Scott et al., Nature Genetics *21*, 440-443, **1999**). Everett et al. disclose a homology-based functional assignment to a putative, mutated sulfate transporter gene (PDS; which encodes "pendrin") identified through positional cloning in Pendred syndrome populations. The homology-based searches were carried out using BLAST and PSI-BLAST with commercial databases using human pendrin as the query sequence. The conclusions of Everett et al. based upon the homology comparisons were that pendrin was a transporter of sulfate. However, experimental studies by Scott et al., clearly demonstrate that pendrin, which has: 1) 29% homology to the rat sulfate-ion transporter encoded by *Sat-1*; 2) 32% homology to the human diastrophic dysplasia sulfate transporter *DTD*; and 3) 45% homology to the human sulfate transporter down-regulated in adenoma encoded by *DRA*, is not a transporter of sulfate, but of chloride and iodine instead.

Secondly, as set forth above, the claimed invention is a genus that encompass a great variety of species which may have distinct different structures due to the recitation of a fragment of 15 nucleotides of SEQ ID NO:635 or nucleic acids hybridizable thereto. One skilled in the art would have serious doubt that these different nucleic acids with different structures would encode protein kinase C.

Given the above and in light of the art recognized fact that minor sequence differences can significantly affect a protein's function, one of skilled in the art would have reasonable doubt that SEQ ID NO:635 does encode a protein kinase C, and would perform further research to reasonably confirm applicants' assertion.

Assuming *arguendo* that the polypeptide encoded by SEQ ID NO:635 were a member of the protein kinase C family, one of skilled in the art would still have to perform further research to determine what specific protein the so-called protein kinase C encoded by SEQ ID NO:635 interacts with and what specific function the protein kinase C has because it has been well known that the protein kinase C family comprises a variety of members with different biological functions including release and exocytosis, cell growth and morphogenesis. See Nishizuka, Y. (Abstract).

In conclusion, since there is a significant question as to whether the claimed nucleic acids encode protein kinase C, applicants could not rely upon a well-established utility for the claimed nucleic acids.

**Claims 67-74 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention lacks a patentable utility due to its not being supported by a specific, substantial, and credible utility or, in the alternative, a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.**

## *Claim Rejections-35 USC § 112*

The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Claims 67-71, 73-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.**

Claims 67-71, 73-74 appear to be drawn to nucleic acid molecules comprising the sequence of SEQ ID NO:635 or 15 contiguous nucleotides thereof, or nucleic acids 90% identical thereto, or nucleic acids that hybridizes thereto, or vector comprising the nucleic acid molecules and recombinant cell comprising such vector.

The claims are rejected mostly for the same reasons as those set forth in the "Revised Interim Written Description Guidelines Training Material" for similar claim limitations. The training material is available on the US PTO's website: http://www.uspto.gov/web/patents/guides.htm, and its relevant sections are attached to this Office action. Please especially see Examples 7, 9-11, and 14.

For example, in regard to claim 67 and its dependent claims, and claims 72 and 74, see example 7 because SEQ ID NO:635 is only a fragment of a full-length open reading frame. Due to the use of "comprising" and the fact that SEQ ID NO:635 is only part of an open reading frame, the claimed nucleic acids read on full-length ORF which is yet to be discovered.

Take as a specific example of claim 68 as to the limitation "hybridizes under stringent condition". The claim is drawn to a genus of polynucleotides including any nucleic acids that hybridize to nucleic acids comprising SEQ ID NO:635, or a 15mer thereof, or 90% identical thereto. Since the claim does not specify any particular stringency conditions (low, medium or

high) for the hybridizations, and do not contain functional limitations, the claim is broad and read on a variety of nucleic acids. Clearly, there is substantial variability among the species encompassed by the scope of the claims because the genus encompasses a variety of species with different structures and distinct functions. While the specification gives an example of the "stringent condition" as 50°C (see page 3), absent a clear definition in the specification, the term is broad and can be including temperatures lower than 50°C. A description of a genus may be achieved by means of a recitation of a representative number of species, falling within the scope of the genus, or by means of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly & Co., 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In the instant case, the specification discloses only a species: the nucleotide sequence of SEQ ID NO:635, but, as set forth above, the lack of a clear stringency of hybridization conditions and the lack of functional limitation in the claims would be expected to yield structurally unrelated nucleic acid molecules. Thus, the single disclosed species is not representative of the genus because there is no structural attribute or feature that is common to the members of the genus.

Similarly, nucleic acids having 90% identity to a polynucleotide comprising the sequence of SEQ ID NO:635 or 15 contiguous nucleotides thereof, encompass species with substantial variation and with unrelated structures that have no structural attribute or features common to all the encompassed species of the claims. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of the genus is not representative of all the species encompassed in the genus, and is insufficient to support the claims.

**Claim 72 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.**

As set forth above, claim 72 is drawn to polynucleotide comprising the nucleotide sequence of the insert of a clone deposited as clone number M00027169D:H06 of ATCC deposit No. PTA-758. The critical limitation in the claim is the sequence of the insert of clone M00027169D:H06 of ATCC deposit No. PTA-758. However, since the address of the depository ATCC is not given, and a statement has not been made that restrictions will be irrevocably removed upon granting of the patent, the clone, and hence the insert thereof, is not accessible to one of skill in the art. Further, while the specification discloses that the sequence of SEQ ID NO:635 is derived from clone M00027169D:H06 (see Table 1A on page 120), there is no indication in the specification that the sequence represents the whole insert of the clone. The specification actually suggests the contrary. Firstly, the specification on page 46 states that more than one sequences listed on Table 1A could be from a same clone (line 10). Secondly, a "validation" re-sequencing of the clone M00027169D:H06 produced the sequence of SEQ ID NO:992, which is much longer than that of SEQ ID NO:635 (718 bp vs 406 bp) indicating the sequence of SEQ ID NO:635 definitely does not represents the whole insert of the clone. Similarly, it is not clear from the specification whether the sequence from the re-sequencing represents the whole insert of the clone.

Given that clone M00027169D:H06 deposited at ATCC is not accessible to one of skill in the art because the deposit has not been perfected, that the whole sequence of the insert is not provided in the specification, and that the sequence of the insert is now known in the prior art, the skilled artisan would not know how to make and thus use the claimed invention. To perfect the deposit, see 37 C.F.R. 1.801-809, MPEP §§ 2410 and 2410.01 and the attached suggestions.

The following is a quotation of the **second** paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 67-71, and 73-74 are rejected under 35 U.S.C. 112 , second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claim 67, as written, can be interpreted as containing three different polynucleotides: **(a)** an "isolated polynucleotide comprising at least 15 contiguous nucleotides of **(b)** a nucleotide sequence having at least 90% sequence identity to **(c)** a sequence selected from the group consisting of SEQ ID NO:635, a degenerate variant of SEQ ID NO:635, and a complement of SEQ ID NO:635.

The metes and bounds of claim 67, as currently written, are not clear. It is unclear what has "at least 90% sequence identity to a sequence selected from the group" of SEQ ID NO:635, a degenerated variant and a complement thereof. Is it (1) the "isolated polynucleotide", (2) the "at least 15 contiguous nucleotides" or (3) the "nucleotide sequence" in the claim? The claimed polynucleotide would be different depending on the answer to the question. For instance, if (3) were right, claim 67 would be interpreted as claiming **(a)** an "isolated polynucleotide comprising

at least 15 contiguous nucleotides of **(b)** a nucleotide sequence having at least 90% sequence identity to **(c)** a sequence selected from the group consisting of SEQ ID NO:635, a degenerate variant of SEQ ID NO:635, and a complement of SEQ ID NO:635". If this were true, one of skill in the art would conclude that the 15 contiguous nucleotides do not have to come from any of the group of SEQ ID NO:635, a degenerated variant thereof and a complement thereof because the 15 contiguous nucleotides could be from a region of **(b)** that is not identical to **(c)** since **(b)** overall is only 90% identical to **(c)**. In the art rejections below, the Office assumes (2) is what is intended by applicants. So claim 67 will be interpreted as claiming a polynucleotide comprising a sequence of at least 15 contiguous nucleotides, which sequence has at least 90% identity to SEQ ID NO:635, a degenerated variant thereof, or a complement thereof.

Claims 68-71 and 73 are rejected due to their dependency from claim 67. The metes and bounds of the claims are unclear for the same reason as that set forth for claim 67.

Claim 74 appears to be drawn to a cDNA obtained by an amplification process using a polynucleotide comprising at least 15 contiguous nucleotides of a nucleotide sequence of SEQ ID NO:635. The metes and bounds of the claim is unclear because it is not apparent what the "polynucleotide comprising at least 15 contiguous nucleotides of a nucleotide sequence of SEQ ID NO:635" is used as in the amplification process, the template or primer. The claimed products can be totally different depending on whether it is used as a template not as a primer in the amplification process. For instance, if the "polynucleotide comprising at least 15 contiguous nucleotides of a nucleotide sequence of SEQ ID NO:635" is used as a template and that the sequence of the polynucleotide outside the 15 contiguous nucleotides of SEQ ID NO:635 has no or very little identity to SEQ ID NO:635 due to the use of the word "comprising" in the claim,

the product of the amplification process could have little, if any, identity to SEQ ID NO:635 should the primer(s) for the amplification be designed to anneal to a region that lies outside the 15 contiguous nucleotides of SEQ ID NO:635 in the polynucleotide.

## *Claim Rejections-35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102(b) that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> ((e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

**Claims 67-71, and 73-74 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hillier et al. (GenBank accession No. R87679.1 (gi: 946492), 8/16/1995).**

As set forth in the rejection of claim 67 under 35 U.S.C. 112, second paragraph, in the present section, claim 67 is interpreted as being drawn to a polynucleotide comprising "at least

15 contiguous nucleotides" and the sequence of the 15 contiguous nucleotides has at least 90% identity to a sequence selected from the group" of SEQ ID NO:635, a degenerated variant and a complement thereof.

In regard to claims 67 and 73, Hillier et al. disclose a cDNA sequence isolated from a human brain cDNA library. The sequence comprises a sequence of at least 15 contiguous nucleotides (actually 89) that has at least 90% (actually 100% identity) to the sequence of SEQ ID NO:635. See GenBank accession No. R87679 and the sequence alignment attached.

In regard to claim 68, given that the sequence of R87679 comprises a sequence of 89 consecutive nucleotides that is 100% identical to the corresponding portion of SEQ ID NO:635, the sequence of R87679 will hybridize to the sequence of SEQ ID NO:635 under stringent conditions such as 50°C and 0.1x SSC as referred to as an example by applicants (page 3 of the specification). A calculation by the examiner using a formula provided in a website (http://www.basic.nwu.edu/biotools/oligocalc.) by North Western University shows that the melting temperature for the sequence of the 89 contiguous nucleotides is 91°C under the salt condition of 0.1x SSC. See the printout of the calculation, and the formula used and references cited therein. It should be pointed out that in the calculation, 10x SSC is considered to contain 3M NaCl. It should be also pointed out that, absent a definition in the specification that states otherwise, hybridization between two polynucleotides is broadly interpreted as including both complete hybridization (i.e. complete base paring) between the two sequences and partial hybridization (i.e. complete base paring). In the instant case, under 50°C and 0.1x SSC, the sequence of R87679 and that of SEQ ID NO:635 will hybridize at least at the portion where the 89 consecutive nucleotides completely match between the two sequences.

Claim 69 is drawn to an antisense molecule comprising at least 15 consecutive nucleotides of SEQ ID NO:635. As set forth above, the nucleic acid molecule disclosed by Hillier et al. comprises at least 15 (actually 89) consecutive nucleotides of SEQ ID NO:635. Thus, the claimed product reads on the polynucleotide molecule disclosed by Hillier et al. It is noted that *In re Spada* discussed a situation where the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). In the instant case, the applicant bears the burden to show that the product of claim 69 and that disclosed by Hillier et al. are not the same. The term "antisense" in the preamble is considered as purpose or intended use and it does not limit the structure of the product. What applicants actually invented is an isolated nucleic acid comprising at least 15 contiguous nucleotides of SEQ ID NO:635. The body of the claim actually fully sets forth all of the limitations of the claimed invention, i.e. the nucleic acid molecule comprising at least 15 contiguous nucleotides of the claimed polynucleotide of claim 67, which is a polynucleotide comprising at least 15 contiguous nucleotides that has at least 90% identity to SEQ ID NO:635, a degenerated variant thereof, or a complement thereof. Thus, the term "antisense" in the preamble only states the purpose or the intended use rather than any distinct limitation of the nucleic acid product. Therefore, the term is of no significance to the structure. Further, the nucleic acid molecule disclosed by Hillier et al. is capable of performing the intended use. The specification on page 18 states that "antisense polynucleotides based on the disclosed polynucleotides will bind and/or interfere with the translation of mRNA comprising a sequence complementary to the antisense polynucleotide". Due to the use of the word "or", it is construed that interfering with the translation of mRNA may not be required for an antisense

polynucleotide. The nucleic acid molecule disclosed by Hillier et al. comprises the complementary sequence of at least 15 consecutive nucleotides of SEQ ID NO:635 which encodes the mRNA for the polypeptide encoded by SEQ ID NO:635, and thus, it would be readily recognized by one of ordinary skill in the art that Hillier et al.'s nucleic acid molecule is capable of binding to the mRNA in light of the melting temperature calculated above. In conclusion, the prior art nucleic acid molecule disclosed by Hillier et al. meets all the claim limitations. Please also see MPEP 2111.02.

In regard to claims 70-71, as set forth above, Hillier et al. disclose that the sequence of R87679 is contained in the vector pT7T3D, and also disclose a host cell containing the vector, DH10B bacterial cell.

Claim 74 is a product by process claim. It is brought to the applicant's attention that a product by process claim is examined for novelty and obviousness of the claimed product only, and that no consideration is given to the novelty or obviousness of the method of making the claimed product. See M.P.E.P. 2113. However, in the instant case, the claimed product, "an isolated cDNA", has no special meaning if separate from the process by which it is made, and, as set forth above, the metes and bounds of the claim is not clear because it is unclear how the "polynucleotide comprising at least 15 contiguous nucleotides of a nucleotide sequence of SEQ ID NO:635" is used in the amplification process, used as a template or primer. Assuming it is used as a primer, it is likely that the product obtained from the process also comprises 15 contiguous nucleotides of a nucleotide sequence of SEQ ID NO:635. As set forth above, the cDNA molecule disclosed by Hillier et al. comprises at least 15 (actually 89) contiguous nucleotides of SEQ ID NO:635. Thus, the claimed product is anticipated by Hillier et al.

**Claims 67-71, and 73-74 are rejected under 35 U.S.C. § 102(e) as being anticipated by Lin et al. (US patent No. 5,712,381, Date of Patent: Jan. 27, 1998, Date of Filing: Aug. 15, 1996).**

As set forth in the rejection of claim 67 under 35 U.S.C. 112, second paragraph, in the present section, claim 67 is interpreted as being drawn to a polynucleotide comprising "at least 15 contiguous nucleotides" and the sequence of the 15 contiguous nucleotides has at least 90% identity to a sequence selected from the group" of SEQ ID NO:635, a degenerated variant and a complement thereof.

In regard to claims 67 and 73, Lin et al. disclose a cDNA molecule, 3DD, isolated from a human mortal fibroblasts, WI38, cDNA library. See column 8. The cDNA molecules comprises a sequence of at least 15 contiguous nucleotides (actually 17) that has at least 90% (actually 100% identity) to the sequence of SEQ ID NO:635. See attached sequence alignment between the instant SEQ ID NO:635 and the SEQ ID NO:3 in Lin et al.

In regard to claim 68, a calculation by the examiner using a formula provided in a website (http://www.basic.nwu.edu/biotools/oligocalc.) by Northwestern University shows that the melting temperature for the sequence of the 17 contiguous nucleotides is 54°C under the salt condition of 0.1x SSC. See the printout of the calculation, and the formula used and references cited therein. As set forth above, absent a definition in the specification that states otherwise, hybridization between two polynucleotides is broadly interpreted as including both complete hybridization (i.e. complete base paring) between the two sequences and partial hybridization (i.e. complete base paring). In the instant case, under 50°C and 0.1x SSC, the sequence of SEQ

ID NO:3 of Lin et al. and that of the instant SEQ ID NO:635 will hybridize at least at the portion where the 17 consecutive nucleotides completely match between the two sequences.

Claim 69 is drawn to an antisense molecule comprising at least 15 consecutive nucleotides of SEQ ID NO:635. As set forth above, the nucleic acid molecule disclosed by Lin et al. comprises at least 15 (actually 17) consecutive nucleotides of SEQ ID NO:635. Thus, the claimed product reads on the polynucleotide molecule disclosed by Lin et al. It is noted that *In re Spada* discussed a situation where the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). In the instant case, the applicant bears the burden to show that the product of claim 69 and that disclosed by Lin et al. are not the same. The term "antisense" in the preamble is considered as purpose or intended use and it does not limit the structure of the product. What applicants actually invented is an isolated nucleic acid comprising at least 15 contiguous nucleotides of SEQ ID NO:635. The body of the claim actually fully sets forth all of the limitations of the claimed invention, i.e. the nucleic acid molecule comprising at least 15 contiguous nucleotides of the claimed polynucleotide of claim 67, which is a polynucleotide comprising at least 15 contiguous nucleotides that has at least 90% identity to SEQ ID NO:635, a degenerated variant thereof, or a complement thereof. Thus, the term "antisense" in the preamble only states the purpose or the intended use rather than any distinct limitation of the nucleic acid product. Therefore, the term is of no significance to the structure. Further, the nucleic acid molecule disclosed by Lin et al. is capable of performing the intended use. The specification on page 18 states that "antisense polynucleotides based on the disclosed polynucleotides will bind and/or interfere with the translation of mRNA comprising a sequence

complementary to the antisense polynucleotide". Due to the use of the word "or", it is construed that interfering with the translation of mRNA may not be required for an antisense polynucleotide. The nucleic acid molecule disclosed by Lin et al. comprises the complementary sequence of at least 15 consecutive nucleotides of SEQ ID NO:635 which encodes the mRNA for the polypeptide encoded by SEQ ID NO:635, and thus, it would be readily recognized by one of ordinary skill in the art that Lin et al.'s nucleic acid molecule is capable of binding to the mRNA in light of the melting temperature calculated above. In conclusion, the prior art nucleic acid molecule disclosed by Lin et al. meets all the claim limitations. Please also see MPEP 2111.02.

In regard to claims 70-71, as set forth above, Lin et al. disclose that the sequence of SEQ ID NO:3 is from a cDNA clone 3DD comprising the vector pJG4-5. Lin et al. also disclose a host cell containing the vector, DH10B bacterial cell. See columns, 8, and 17-18.

Claim 74 is a product by process claim. It is brought to the applicant's attention that a product by process claim is examined for novelty and obviousness of the claimed product only, and that no consideration is given to the novelty or obviousness of the method of making the claimed product. See M.P.E.P. 2113. However, in the instant case, the claimed product, "an isolated cDNA", has no special meaning if separate from the process by which it is made, and, as set forth above, the metes and bounds of the claim is not clear because it is unclear how the "polynucleotide comprising at least 15 contiguous nucleotides of a nucleotide sequence of SEQ ID NO:635" is used in the amplification process, used as a template or primer. Assuming it is used as a primer, it is likely that the product obtained from the process also comprises 15 contiguous nucleotides of a nucleotide sequence of SEQ ID NO:635. As set forth above, the

cDNA molecule disclosed by Lin et al. comprises at least 15 (actually 17) contiguous nucleotides of SEQ ID NO:635. Thus, the claimed product is anticipated by Lin et al.

## *Conclusion*

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to:
Shubo "Joe" Zhou, Ph.D., whose telephone number is (703) 605-1158. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst Tina Plunkett whose telephone number is 703)-305-3524, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

Shubo "Joe" Zhou, Ph.D.
Patent Examiner

ATTACHMENT

## SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant or assignee, or a statement by applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address.

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent.

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. 1.14 and 35 U.S.C. § 122.

6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer.

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

GenCore version 5.1.4_p5_4578


M nucleic - nucleic search, using sw model

un on: May 27, 2003, 17:14:02 ; Search time 1894 Seconds
(without alignments)
6238.511 Million cell updates/sec

itle: US-09-404-706A-635
erfect score: 406
equence: 1 ccgcctccgtcgcacagtcg.....tacctgcgcggccagcacat 406

coring table: IDENTITY_NUC
Gapop 10.0 , Gapext 1.0

earched: 2054640 seqs, 14551402878 residues

otal number of hits satisfying chosen parameters: 4109280

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

ost-processing: Minimum Match 0%
Maximum Match 100%
Listing first 100 summaries

atabase : GenEmbl:*
1: gb_ba:*
2: gb_htg:*
3: gb_in:*
4: gb_om:*
5: gb_ov:*
6: gb_pat:*
7: gb_ph:*
8: gb_pl:*
9: gb_pr:*
10: gb_ro:*
11: gb_sts:*
12: gb_sy:*
13: gb_un:*
14: gb_vi:*
15: em_ba:*
16: em_fun:*
17: em_hum:*
18: em_in:*
19: em_mu:*
20: em_om:*
21: em_or:*
22: em_ov:*
23: em_pat:*
24: em_ph:*
25: em_pl:*
26: em_ro:*
27: em_sts:*
28: em_un:*
29: em_vi:*
30: em_htg_hum:*
31: em_htg_inv:*
32: em_htg_other:*
33: em_htg_mus:*
34: em_htg_pln:*
35: em_htg_rod:*
36: em_htg_mam:*
37: em_htg_vrt:*
38: em_sy:*
39: em_htgo_hum:*
40: em_htgo_mus:*
41: em_htgo_other:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

| Result No. | | Score | % Query Match | Length | DB | ID | Description |
|---|---|---|---|---|---|---|---|
| 1 | | 406 | 100.0 | 1868 | 9 | AK057849 | AK057849 Homo sapi |
| 2 | | 372.4 | 91.7 | 1640 | 6 | AX179651 | AX179651 Sequence |
| 3 | | 372.4 | 91.7 | 1787 | 6 | AX056359 | AX056359 Sequence |
| 4 | | 372.4 | 91.7 | 1858 | 9 | BC015792 | BC015792 Homo sapi |
| 5 | | 367.4 | 90.5 | 2182 | 6 | AX364903 | AX364903 Sequence |
| 6 | | 353 | 86.9 | 2038 | 9 | AB056389 | AB056389 Macaca fa |
| 7 | | 319.6 | 78.7 | 2184 | 10 | BC026457 | BC026457 Mus muscu |
| 8 | | 319.6 | 78.7 | 2201 | 10 | AB041542 | AB041542 Mus muscu |
| 9 | | 317.8 | 78.3 | 2150 | 9 | AK098366 | AK098366 Homo sapi |
| 10 | | 317.4 | 78.2 | 1092 | 6 | AX428279 | AX428279 Sequence |
| 11 | | 284.2 | 70.0 | 2045 | 10 | MMU250840 | AJ250840 Mus muscu |
| 12 | | 271.8 | 66.9 | 3244 | 6 | AX376504 | AX376504 Sequence |
| 13 | | 269.8 | 66.5 | 3224 | 6 | AX056360 | AX056360 Sequence |
| 14 | | 269.8 | 66.5 | 3224 | 9 | HSA250839 | AJ250839 Homo sapi |
| 15 | | 239.6 | 59.0 | 678 | 6 | AX303179 | AX303179 Sequence |
| 16 | | 239.6 | 59.0 | 711 | 6 | AX303181 | AX303181 Sequence |
| 17 | | 239.6 | 59.0 | 827 | 9 | BC021666 | BC021666 Homo sapi |
| 18 | | 239.6 | 59.0 | 981 | 6 | AX166513 | AX166513 Sequence |
| 19 | | 239.6 | 59.0 | 1191 | 6 | AX303185 | AX303185 Sequence |
| 20 | | 239.6 | 59.0 | 1191 | 6 | AX320936 | AX320936 Sequence |
| 21 | | 239.6 | 59.0 | 1224 | 6 | AX303183 | AX303183 Sequence |
| 22 | | 239.6 | 59.0 | 1281 | 6 | AX320934 | AX320934 Sequence |
| 23 | | 239.6 | 59.0 | 1594 | 6 | AX207388 | AX207388 Sequence |
| 24 | | 239.6 | 59.0 | 1675 | 6 | AX303187 | AX303187 Sequence |
| 25 | | 239.6 | 59.0 | 2063 | 9 | AK094580 | AK094580 Homo sapi |
| 26 | c | 166.2 | 40.9 | 145630 | 9 | AL512622 | AL512622 Human DNA |
| 27 | | 143.6 | 35.4 | 287323 | 2 | AC093363 | AC093363 Mus muscu |
| 28 | | 128 | 31.5 | 62263 | 2 | AC100239 | AC100239 Mus muscu |
| 29 | c | 124.4 | 30.6 | 175066 | 2 | AC115152 | AC115152 Rattus no |
| 30 | | 124 | 30.5 | 604 | 3 | CFA298057 | AJ298057 Crithidia |
| 31 | | 121.2 | 29.9 | 138504 | 9 | AC092665 | AC092665 Homo sapi |
| 32 | | 119.6 | 29.5 | 183977 | 2 | AC097956 | AC097956 Rattus no |
| 33 | | 116.2 | 28.6 | 3811 | 3 | LMU91743 | U91743 Leishmania |
| 34 | | 116.2 | 28.6 | 36068 | 3 | AC012051 | AC012051 Leishmani |
| 35 | | 115.8 | 28.5 | 2333 | 3 | LMA297564 | AJ297564 Leishmani |
| 36 | c | 115.8 | 28.5 | 37778 | 3 | AC009602 | AC009602 Leishmani |
| 37 | | 115.4 | 28.4 | 1619 | 4 | AF238980 | AF238980 Ovis arie |
| 38 | | 115.4 | 28.4 | 1624 | 4 | AF238979 | AF238979 Ovis arie |
| 39 | | 115.2 | 28.4 | 107325 | 9 | AC009189 | AC009189 Homo sapi |
| 40 | | 115 | 28.3 | 5887 | 9 | AB011133 | AB011133 Homo sapi |
| 41 | | 114.6 | 28.2 | 838 | 3 | LMA297954 | AJ297954 Leishmani |
| 42 | c | 112.8 | 27.8 | 196859 | 9 | AC096740 | AC096740 Homo sapi |
| 43 | | 112.2 | 27.6 | 2522 | 4 | BTPKINCA | X67154 B.taurus mR |
| 44 | | 110.8 | 27.3 | 1788 | 6 | A84453 | A84453 Sequence 68 |
| 45 | | 110.8 | 27.3 | 1788 | 6 | AX427352 | AX427352 Sequence |
| 46 | | 110.8 | 27.3 | 2137 | 10 | RNPKCA1 | X57986 Rat mRNA fo |
| 47 | | 110.8 | 27.3 | 2231 | 10 | MUSPKCD | M12303 Mouse cAMP- |
| 48 | | 110.8 | 27.3 | 2257 | 10 | CRUPROKINA | M63311 Chinese ham |
| 49 | | 110.8 | 27.3 | 2292 | 10 | BC003238 | BC003238 Mus muscu |
| 50 | | 110.6 | 27.2 | 2181 | 6 | A84455 | A84455 Sequence 70 |
| 51 | | 110.6 | 27.2 | 2181 | 6 | AX427354 | AX427354 Sequence |
| 52 | | 110.6 | 27.2 | 2184 | 6 | A84523 | A84523 Sequence 13 |
| 53 | | 110.6 | 27.2 | 2184 | 6 | AX427422 | AX427422 Sequence |
| 54 | | 110.6 | 27.2 | 2610 | 6 | A62733 | A62733 Sequence 3 |
| 55 | | 110.6 | 27.2 | 2610 | 6 | A63232 | A63232 Sequence 1 |
| 56 | | 110.6 | 27.2 | 2610 | 6 | AR076381 | AR076381 Sequence |
| 57 | | 110.6 | 27.2 | 2610 | 9 | HUMRACPC | M63167 Human rac p |
| 58 | | 110.6 | 27.2 | 2738 | 9 | BC000479 | BC000479 Homo sapi |
| 59 | c | 109.6 | 27.0 | 110000 | 2 | LMFLCHR31_12 | Continuation (13 o |
| 60 | | 109.2 | 26.9 | 2231 | 8 | AF041843 | AF041843 Ustilago |
| 61 | | 107.4 | 26.5 | 1337 | 8 | BSIPROKINC | M81709 Blastocladi |
| 62 | | 107.4 | 26.5 | 1635 | 6 | AX409693 | AX409693 Sequence |
| 63 | | 107.4 | 26.5 | 1635 | 9 | HUMPRKACG | M34182 Human testi |
| 64 | | 107.4 | 26.5 | 4357 | 9 | HSAJ1597 | AJ001597 Homo sapi |
| 65 | c | 107.4 | 26.5 | 171381 | 9 | AL162730 | AL162730 Human DNA |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 66 | 107 | 26.4 | 1691 | 4 | BTPKB |
| | 67 | 106 | 26.1 | 3412 | 9 | AB028019 |
| | 68 | 106 | 26.1 | 4098 | 9 | AF207547 |
| | 69 | 106 | 26.1 | 5486 | 6 | E38226 |
| | 70 | 106 | 26.1 | 5486 | 6 | E38227 |
| c | 71 | 106 | 26.1 | 183597 | 9 | AL356285 |
| | 72 | 104.6 | 25.8 | 1054 | 4 | AF525132 |
| | 73 | 104.6 | 25.8 | 1056 | 4 | AF367428 |
| | 74 | 104.2 | 25.7 | 2776 | 9 | AK027123 |
| | 75 | 104.2 | 25.7 | 2945 | 9 | AK096519 |
| | 76 | 104.2 | 25.7 | 4049 | 9 | AB018350 |
| | 77 | 104.2 | 25.7 | 4087 | 9 | BC015816 |
| | 78 | 104.2 | 25.7 | 5737 | 9 | AB047005 |
| | 79 | 103.4 | 25.5 | 4833 | 9 | AB023190 |
| | 80 | 103.4 | 25.5 | 4885 | 6 | AX405753 |
| | 81 | 103 | 25.4 | 2305 | 8 | NCCOT1 |
| | [illegible] | | | | | |
| | 83 | 102.6 | 25.3 | 936 | 9 | HUMPKACATO |
| | 84 | 102.6 | 25.3 | 2324 | 4 | BOVPKIC |
| | 85 | 102.6 | 25.3 | 2549 | 6 | AX411047 |
| | 86 | 102.6 | 25.3 | 2549 | 9 | HSPKA |
| | [illegible] | 101.8 | 25.1 | 2810 | 3 | AY069425 |
| | | 101.8 | 25.1 | 3226 | 3 | DMDC0 |
| | | 101.8 | 25.1 | 3959 | 3 | DROCAPKCA |
| | 90 | 101.8 | 25.1 | 167596 | 2 | AC013177 |
| | 91 | 101.8 | 25.1 | 176075 | 3 | AC007291 |
| | 92 | 101.8 | 25.1 | 183007 | 3 | AC007257 |
| c | 93 | 101.8 | 25.1 | 260624 | 3 | AE003625 |
| | 94 | 101.2 | 24.9 | 1103 | 3 | GCPKC2GEN |
| | 95 | 101 | 24.9 | 629 | 9 | MMAJ1927 |
| | 96 | 101 | 24.9 | 1513 | 10 | MUSRAC |
| | 97 | 101 | 24.9 | 1617 | 10 | RATRPKAA |
| | 98 | 100 | 24.6 | 3155 | 6 | AR201457 |
| | 99 | 100 | 24.6 | 3460 | 10 | AB023958 |
| | 100 | 99.4 | 24.5 | 1254 | 9 | HSPKBR |

| | |
|---|---|
| X61036 | B.taurus mR |
| AB028019 | Homo sapi |
| AF207547 | Homo sapi |
| E38226 | Human tumor |
| E38227 | Human tumor |
| AL356285 | Human DNA |
| AF525132 | Canis fam |
| AF367428 | Oryctolag |
| AK027123 | Homo sapi |
| AK096519 | Homo sapi |
| AB018350 | Homo sapi |
| BC015816 | Homo sapi |
| AB047005 | Homo sapi |
| AB023190 | Homo sapi |
| AX405753 | Sequence |
| X97657 | N.crassa mR |
| [illegible] | |
| AF208004 | Homo sapi |
| M80335 | Homo sapien |
| M13978 | Bovine prot |
| AX411047 | Sequence |
| X07767 | Human mRNA |
| AY069425 | Drosophil |
| X16969 | Drosophila |
| M18655 | D.melanogas |
| AC013177 | Drosophil |
| AC007291 | Drosophil |
| AC007257 | Drosophil |
| AE003625 | Drosophil |
| X87683 | G.cydonium |
| AJ001927 | Macaca mu |
| M94335 | Mus musculu |
| D30040 | Rat mRNA fo |
| AR201457 | Sequence |
| AB023958 | Mus muscu |
| X61037 | H.sapiens m |

ALIGNMENTS

RESULT 1
AK057849
LOCUS AK057849 1868 bp mRNA linear PRI 31-OCT-2001
DEFINITION Homo sapiens cDNA FLJ25120 fis, clone CBR06020.
ACCESSION AK057849
VERSION AK057849.1 GI:16553810
KEYWORDS oligo capping; fis (full insert sequence).
SOURCE Homo sapiens brain cDNA to mRNA, clone_lib:CBR clone:CBR06020.
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1
AUTHORS Tashiro,H., Yamazaki,M., Watanabe,K., Kumagai,A., Itakura,S., Fukuzumi,Y., Fujimori,Y., Komiyama,M., Suzuki,Y., Hata,H., Nakagawa,K., Mizuno,S., Morinaga,M., Kawamura,M., Sugiyama,T., Irie,R., Otsuki,T., Sato,H., Nishikawa,T., Sugiyama,A., Kawakami,B., Nagai,K., Isogai,T. and Sugano,S.
TITLE NEDO human cDNA sequencing project
JOURNAL Unpublished
REFERENCE 2 (bases 1 to 1868)
AUTHORS Sugano,S. and Suzuki,Y.
TITLE Direct Submission
JOURNAL Submitted (24-OCT-2001) Sumio Sugano, Institute of Medical Science, University of Tokyo, Laboratory of Genome Structure, Human Genome Center; Shirokane-dai, 4-6-1, Minato-ku, Tokyo 108-8639, Japan (E-mail:cdnal@ims.u-tokyo.ac.jp, Tel:81-3-5449-5286, Fax:81-3-5449-5416)
COMMENT NEDO human cDNA sequencing project supported by Ministry of Economy, Trade and Industry of Japan; cDNA full insert sequencing: Research Association for Biotechnology (RAB); cDNA library construction and 5'-end one pass sequencing: Institute of Medical Science, University of Tokyo, Laboratory of Genome Structure, Human Genome Center; 3'-end one pass sequencing: RAB; clone selection for full insert sequencing: RAB and Helix Research Institute.
FEATURES Location/Qualifiers
source 1. .1868
/organism="Homo sapiens"
/db_xref="taxon:9606"
/clone="CBR06020"
/tissue_type="brain"
/clone_lib="CBR"
/note="cloning vector: pME18SFL3"
BASE COUNT 369 a 556 c 603 g 340 t
ORIGIN

Query Match 100.0%; Score 406; DB 9; Length 1868;
Best Local Similarity 100.0%; Pred. No. 1.8e-53;
Matches 406; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy       1 CCGCCTCCGTCGCACAGTCGGGAGGCTTTGCAGTGAACTTCGACCACTTCCAGATCCTTC 60
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      47 CCGCCTCCGTCGCACAGTCGGGAGGCTTTGCAGTGAACTTCGACCACTTCCAGATCCTTC 106

Qy      61 GGGCCATTGGGAAGGGCAGCTTTGGCAAGGTGTGCATTGTGCAGAAGCGGGACACGGAGA 120
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     107 GGGCCATTGGGAAGGGCAGCTTTGGCAAGGTGTGCATTGTGCAGAAGCGGGACACGGAGA 166

Qy     121 AGATGTACGCCATGAAGTACATGAACAAGCAGCAGTGCATCGAGCGCGACGAGGTCCGCA 180
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     167 AGATGTACGCCATGAAGTACATGAACAAGCAGCAGTGCATCGAGCGCGACGAGGTCCGCA 226

Qy     181 ACGTCTTCCGGGAGCTGGAGATCCTGCAGGAGATCGAGCACGTCTTCCTGGTGAACCTCT 240
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     227 ACGTCTTCCGGGAGCTGGAGATCCTGCAGGAGATCGAGCACGTCTTCCTGGTGAACCTCT 286

Qy     241 GGTACTCCTTCCAGGACGAGGAGGACATGTTCATGGTCGTGGACCTGCTACTGGGCGGGG 300
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     287 GGTACTCCTTCCAGGACGAGGAGGACATGTTCATGGTCGTGGACCTGCTACTGGGCGGGG 346

Qy     301 ACCTGCGCTACCACCTGCAGCAGAACGTGCAGTTCTCCGAGGACACAGTGAGGCTGTACA 360
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     347 ACCTGCGCTACCACCTGCAGCAGAACGTGCAGTTCTCCGAGGACACAGTGAGGCTGTACA 406

Qy     361 TCTGCGAGATGGCACTGGCTCTGGACTACCTGCGCGGCCAGCACAT 406
             |||||||||||||||||||||||||||||||||||||||||||||
Db     407 TCTGCGAGATGGCACTGGCTCTGGACTACCTGCGCGGCCAGCACAT 452
```

RESULT 2
AX179651
LOCUS AX179651 1640 bp DNA linear PAT 06-AUG-2001
DEFINITION Sequence 24 from Patent WO0146397.
ACCESSION AX179651
VERSION AX179651.1 GI:15132072
KEYWORDS
SOURCE human.
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 1640)
AUTHORS Yang,J., Baughn,M.R., Burford,N., Au-Young,J., Lu,D.A., Reddy,R., Yue,H., Yao,M.G., Lal,P. and Khan,F.A.
TITLE Human kinases
JOURNAL Patent: WO 0146397-A 24 28-JUN-2001; Incyte Genomics, Inc. (US)
FEATURES Location/Qualifiers
source 1. .1640
/organism="Homo sapiens"
/db_xref="taxon:9606"
/note="Incyte ID No: 3244919CB1"
BASE COUNT 316 a 524 c 530 g 270 t
ORIGIN

Query Match 91.7%; Score 372.4; DB 6; Length 1640;
Best Local Similarity 99.7%; Pred. No. 2.8e-48;
Matches 373; Conservative 0; Mismatches 1; Indels 0; Gaps 0;

L3 ANSWER 11 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:253637 CAPLUS
DOCUMENT NUMBER: 138:382923
TITLE: Endothelial cell dysfunction in type I and II diabetes: The cellular basis for dysfunction
AUTHOR(S): Pannirselvam, Malarvannan; Anderson, Todd J.; Triggle, Chris R.
CORPORATE SOURCE: Department of Pharmacology and Therapeutics, Faculty of Medicine, and Smooth Muscle Research Group, University of Calgary, Calgary, AB, Can.
SOURCE: Drug Development Research (**2003**), 58(1), 28-41
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**
AB A review. Micro- and macrovascular complications are the leading causes of mortality in Types I and II diabetes. Hyperglycemia results in increased advanced glycosylation end (AGE) products, oxidative stress, increased sorbitol levels, and increased activation of **protein kinase C**. These effects of hyperglycemia eventually lead to impaired endothelium-dependent relaxation to vasoactive substances such as acetylcholine and bradykinin. Increased oxidative stress, which will reduce levels of nitric oxide (NO), and/or decreased bioavailability of tetrahydrobiopterin (BH4), a cofactor for endothelial NO synthase (eNOS), may lead to a phenomenon called "uncoupling" of eNOS and this leads to endothelial dysfunction. Uncoupled NOS produces superoxide anions which lead to a further redn. in NO bioavailability. Thus, restoring BH4 levels and antioxidant activity could prove to be novel approaches for the treatment of endothelial dysfunction in Type I and II diabetes.
REFERENCE COUNT: 170 THERE ARE 170 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:253410 CAPLUS
DOCUMENT NUMBER: 138:366429
TITLE: **Protein kinase C** modulates pulmonary endothelial permeability: A paradigm for acute lung injury
AUTHOR(S): Siflinger-Birnboim, Alma; Johnson, Arnold
CORPORATE SOURCE: Research Service, Stratton Veterans Affairs Medical Center, The Albany Medical College, Albany, NY, 12208, USA
SOURCE: American Journal of Physiology (**2003**), 284(3, Pt. 1), L435-L451
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**
AB A review. The intracellular serine/threonine kinase **protein kinase C** (PKC) has an important role in the genesis of pulmonary edema. This review discusses the PKC-mediated mechanisms that participate in the pulmonary endothelial response to agents involved in lung injury characteristic of the respiratory distress syndrome. Thus the paradigms of PKC-induced lung injury are discussed within the context of pulmonary trans-vascular fluid exchange. We focus on the signal transduction pathways that are modulated by PKC and their effect on lung endothelial permeability. Specifically, .alpha.-thrombin, tumor necrosis factor (TNF)-.alpha., and reactive oxygen species are discussed because of their well-established roles in both human and exptl. lung injury. We conclude that PKC, most likely PKC-.alpha., is a primary supporter for lung endothelial injury in response to .alpha.-thrombin, TNF-.alpha., and

reactive oxygen species.
REFERENCE COUNT: 201 THERE ARE 201 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:252552 CAPLUS
DOCUMENT NUMBER: 138:382915
TITLE: Progression of diabetic nephropathy
AUTHOR(S): Kikkawa, Ryuichi; Koya, Daisuke; Haneda, Masakazu
CORPORATE SOURCE: Third Department of Medicine, Shiga University of Medical Science, Shiga, Japan
SOURCE: American Journal of Kidney Diseases (**2003**), 41(3, Suppl. 1), S19-S21
CODEN: AJKDDP; ISSN: 0272-6386
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**
AB A review on the authors' own work. Background: Diabetic nephropathy, a kidney disease caused by diabetes, is the most devastating and money-consuming complication in patients with diabetes throughout the world. The cardinal lesion of diabetic nephropathy resides in renal glomeruli and is called diabetic glomerulosclerosis. Hyperglycemia is responsible for the development and progression of diabetic nephropathy through metabolic derangements, including increased oxidative stress, renal polyol formation, activation of **protein kinase C** (PKC)-mitogen-activated protein kinases (MAPKs), and accumulation of advanced glycation end products, as well as such hemodynamic factors as systemic hypertension and increased intraglomerular pressure. Methods: The authors examd. whether inhibition of the PKC-MAPK pathway could inhibit functional and pathol. abnormalities in glomeruli from diabetic animal models and cultured mesangial cells exposed to high glucose condition and/or mech. stretch. Results: Direct inhibition of PKC by PKC .beta. inhibitor prevented albuminuria and mesangial expansion in db/db mice, a model of type 2 diabetes. The authors also found that inhibition of MAPK by PD98059, an inhibitor of MAPK, or mitogen-activated extracellular regulated protein kinase kinase prevented enhancement of activated protein-1 (AP-1) DNA binding activity and fibronectin expression in cultured mesangial cells exposed to mech. stretch in an in vivo model of glomerular hypertension. Conclusion: These findings highlight the important role of PKC-MAPK pathway activation in mediating the development and progression of diabetic nephropathy.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:246207 CAPLUS
DOCUMENT NUMBER: 138:382908
TITLE: Variations of human adrenomedullin gene and its relation to cardiovascular diseases
AUTHOR(S): Ishimitsu, Toshihiko; Tsukada, Kohju; Minami, Junichi; Ono, Hidehiko; Matsuoka, Hiroaki
CORPORATE SOURCE: Department of Hypertension and Cardiorenal Medicine, Dokkyo University School of Medicine, Tochigi, Japan
SOURCE: Hypertension Research (**2003**), 26(Suppl.), S129-S134
CODEN: HRESE4; ISSN: 0916-9636
PUBLISHER: Japanese Society of Hypertension
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**
AB A review. The studies concerning the structure and variations of the human adrenomedullin (AM) gene are reviewed, and their relations to the gene function and genetic predisposition to cardiovascular diseases are discussed. The genomic human AM gene is composed of 4 exons, and the

whole nucleotide sequence corresponding to mature AM resides in the 4th exon. In chromosomal sublocalization, the AM gene is located in the distal portion of the short arm of chromosome 11 (11p15.1-3). Anal. of the promoter region of the AM gene has revealed that 2 transcription factors, nuclear factor for interleukin-6 expression (NF-IL6) and activator protein 2 (AP-2), participate in the regulation of AM gene expression. It is surmised that NF-IL6 mediates inflammatory stimuli and AP-2 mediates signals of phospholipase C and **protein kinase C** activation. In addn. to these factors, hypoxia induces AM gene expression via the hypoxia inducible factor-1 (HIF-1) binding site. The 3'-end of the AM gene is flanked by a microsatellite marker of cytosine adenine (CA) repeats. In Japanese, there are 4 types of alleles with different CA-repeat nos.: 11, 13, 14 and 19. It is suggested that existence of the 19-repeat allele is assocd. with genetic predispositions to develop essential hypertension and diabetic nephropathy.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:246143 CAPLUS
DOCUMENT NUMBER: 138:384549
TITLE: Cancer-related cellular and molecular effects of phytoestrogens
AUTHOR(S): Alink, Gerrit M.; Dopp, Elke
CORPORATE SOURCE: Division of Toxicology, Wageningen University, Neth.
SOURCE: Natural and Synthetic Estrogens: Aspects of the Cellular and Molecular Activity (**2002**), 57-75. Editor(s): Dopp, Elke; Stopper, Helga; Alink, Gerrit M. Research Signpost: Trivandrum, India. CODEN: 69DSC6; ISBN: 81-7736-138-4
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: **English**

AB A review. Estrogens are related to different types of cancer like breast, prostate and endometrial cancer. Phytoestrogens, however, are mostly considered to be protective against certain cancers like e.g. breast cancer. The mechanisms by which these phytoestrogens influence cancer are still in debate. This review summarizes possible mechanisms by which these compds. may modulate the cancer process. Considered are 1) estrogen receptor (ER)-mediated effects, 2) effects on cellular proteins, enzymes and growth factors, and 3) genomic and apoptosis-inducing effects. At low concns. (below 10 .mu.M) phytoestrogens may stimulate cell proliferation, while at high concns. cell proliferation is inhibited. Stimulation of cell proliferation seems to be ER-mediated, implying pS2 and AP-1 activation, while inhibition is ER-independent. Phytoestrogens may interact with key enzymes in estrogen biosynthesis and with phase II detoxification enzymes (QR). Genistein can effectively inhibit three different protein kinases: tyrosine kinase, src family kinases and **protein kinase C** (PKC). It seems to be relevant for PKC-activity that genistein, daidzein and coumestrol increase [Ca2+]i. Genistein down-regulates matrix metalloproteinase (MMP-9), which inhibits tumor invasion. The phytoestrogen genistein antagonizes growth stimulatory EGF and TGF.alpha. signaling, whereas TGF.alpha. can also act synergistically with phytoestrogens in accelerating cancer cell growth. Genistein stimulates growth inhibitory TGF.beta. expression, and decreases TGF.beta.-mediated angiogenesis. Furthermore genistein inhibits induction of stress proteins (GRP and HSP). A marked genomic effect is that coumestrol and genistein are able to induce clastogenicity and/or mutagenicity by inhibition of DNA topoisomerase II. Further daidzein but not genistein can enhance BRCA1 expression. Genistein produces cell cycle arrest and apoptosis in different tumor cells. The mol. mechanisms for induction of cell cycle arrest and apoptosis might be the inhibition of cyclin B1 and NF-.vkappa.B, and up-regulation of Bax-2, p53 and p21. The relevance of the biphasic effects of phytoestrogens, and the mol.

mechanisms in relation to cancer are discussed.
REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:241386 CAPLUS
DOCUMENT NUMBER: 138:366403
TITLE: Diabetic microangiopathy: Pathology and current understanding of its pathogenesis
AUTHOR(S): Yagihashi, S.; Wada, R.; Yamagishi, S.
CORPORATE SOURCE: Department of Pathology, Hirosaki University School of Medicine, Japan
SOURCE: Verhandlungen der Deutschen Gesellschaft fuer Pathologie (**2002**), 86(Pathologie der Niere und der Ableitenden Harnwege Molekulare Gefaesspathologie und Angiogenese), 91-100
CODEN: VDGPAN; ISSN: 0070-4113
PUBLISHER: Urban & Fischer Verlag GmbH & Co. KG
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**
AB A review. Recent drastic increase in diabetic population poses serious problems in both health sciences and socioeconomic conditions. The most important issue in the clin. practice of diabetic patients is the treatment and care of chronic complications. It is not fully clear, however, as to the pathophysiol. of diabetic microangiopathy and its pathogenesis. Recent studies on microvessel pathol. in diabetic patients and mol. analyses on the diabetic animal models disclosed novel features of the dynamic changes of specific organ pathol. affected by diabetes and factors involved in its pathogenesis. Under long-term hyperglycemia, early stimuli elicit adaptive reactions of tissues showing acute inflammatory processes of vessel walls and then late irreversible and regressive changes of microangiopathy. Consequently, remodeling of vascular cells and excessive matrix prodn. are cardinal feature. The precise mechanisms of how these tissue changes occur remain speculative; increased polyol pathway, excessive non-enzymic glycation, increased **protein kinase C** activity, as well as oxidative stress are all interrelated for the cause and development of the microangiopathy.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:237790 CAPLUS
DOCUMENT NUMBER: 138:397931
TITLE: The structure and function of PKN, a protein kinase having a catalytic domain homologous to that of PKC
AUTHOR(S): Mukai, Hideyuki
CORPORATE SOURCE: Biosignal Research Center, Kobe University, Kobe, 657-8501, Japan
SOURCE: Journal of Biochemistry (Tokyo, Japan) (**2003**), 133(1), 17-27
CODEN: JOBIAO; ISSN: 0021-924X
PUBLISHER: Japanese Biochemical Society
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**
AB A review. PKN kinase is a serine/threonine protein kinase that has a catalytic domain homologous to **protein kinase C** (PKC) family members and a unique regulatory region contg. antiparallel coiled-coil (ACC) domains. PKN kinase is the 1st identified serine/threonine protein kinase that can bind to and be activated by small GTPase Rho, and it can also be activated by fatty acids such as arachidonic acid in vitro. PKN kinase is widely distributed in various organisms such as mammal, frog, fly, and starfish. There are at least 3 different isoforms of PKN kinase (PKN.alpha./PAK-1/PRK-1, PKN.beta., and

PRK2/PAK-2/PKN.gamma.) in mammals, each of which shows different enzymol. properties, tissue distribution, and varied functions.
REFERENCE COUNT: 123 THERE ARE 123 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 18 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:237789 CAPLUS
DOCUMENT NUMBER: 138:397930
TITLE: **Protein kinase C** .lambda./.iota. (PKC.lambda./.iota.): A PKC isotype essential for the development of multicellular organisms
AUTHOR(S): Suzuki, Atsushi; Akimoto, Kazunori; Ohno, Shigeo
CORPORATE SOURCE: Department of Molecular Biology, Yokohama City University School of Medicine, Yokohama, 239-0004, Japan
SOURCE: Journal of Biochemistry (Tokyo, Japan) (**2003**), 133(1), 9-16
CODEN: JOBIAO; ISSN: 0021-924X
PUBLISHER: Japanese Biochemical Society
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**
AB A review. **Protein kinase C** isoform .lambda./.iota. (PKC-.lambda./.iota.) belongs to the 3rd group of the PKC family, atypical PKC (aPKC), together with PKC-.xi., based on its sequence divergence from conventional and novel PKCs obsd. not only in the N-terminal regulatory domain but also in the kinase domain. Although one of the most distinct features of aPKC is its single, unrepeated cysteine-rich domain, recent studies have revealed that the N-terminal regulatory domain has addnl. aPKC-specific structural motifs involved in various protein-protein interactions, which are important for the regulation and the subcellular targeting of aPKC. The identification of aPKC-specific binding proteins has significantly facilitated the understanding of the activation mechanism as well as the physiol. function of aPKC at the mol. level. In particular, the finding that the mammalian homologs of the Caenorhabditis elegans proteins, PAR-3 and PAR-6, bind aPKC unexpectedly opens a new avenue for exploring a thus far completely unrecognized crit. function of aPKC, i.e., as a component of an evolutionarily conserved cell polarity machinery. Together with the great progress in the genome project as well as in the genetic anal. of model organisms, these advances are leading researchers into the new era of aPKC study in which functional divergence between PKC-.lambda./.iota. and PKC-.xi. can be discussed and elaborated.
REFERENCE COUNT: 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 19 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:237788 CAPLUS
DOCUMENT NUMBER: 138:397929
TITLE: **Protein kinase C**.xi. (PKC.xi.): Activation mechanisms and cellular functions
AUTHOR(S): Hirai, Takaaki; Chida, Kazuhiro
CORPORATE SOURCE: Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo, 113-8657, Japan
SOURCE: Journal of Biochemistry (Tokyo, Japan) (**2003**), 133(1), 1-7
CODEN: JOBIAO; ISSN: 0021-924X
PUBLISHER: Japanese Biochemical Society
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**
AB A review. **Protein kinase C** isoform .xi. (PKC-.xi.) is a member of the atypical PKC subfamily and has been widely

implicated in the regulation of cellular functions. Increasing evidence from studies using in vitro and in vivo systems points to PKC-.xi. as a key regulator of crit. intracellular signaling pathways induced by various extracellular stimuli. The major activation pathway of PKC-.xi. depends on phosphatidylinositol (PI)-3,4,5-trisphosphate (PIP3), which is mainly produced by PI-3 kinase. 3'-PI-dependent protein kinase 1, which binds with high affinity to PIP3, phosphorylates and activates PKC-.xi.. Many studies have demonstrated the involvement of PKC-.xi. in the MAP kinase cascade, transcriptional factor NF.kappa.B activation, ribosomal protein S6 kinase signaling, and cell polarity. An important mol. event in a cell is the assocn. of PKC-.xi. with other signaling mols., as well as scaffold proteins, to form large complexes that regulate their pathways. The understanding of the mechanisms underlying PKC-.xi.-mediated control of intracellular signaling is beginning to provide important insights into the roles of PKC-.xi. in various cells.

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:223583 CAPLUS
DOCUMENT NUMBER: 138:367966
TITLE: Role of N-3 polyunsaturated fatty acids in the modulation of T-cell signalling
AUTHOR(S): Khan, N. A.; Hichami, A.
CORPORATE SOURCE: UPRES Lipids and Nutrition, Faculty of Life Sciences, Universite de Bourgogne, Dijon, 21000, Fr.
SOURCE: Recent Research Developments in Lipids (**2002**), 6, 65-78
CODEN: RRDLBH
PUBLISHER: Transworld Research Network
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**

AB A review. T-cell activation involves a series of complex mechanisms from membrane receptor to gene transcription via the second messenger cascades. T-cell proliferation can be divided into two sets of events; early and late. The early events are part of first 15 or 30 min of cell activation, whereas the late events may last long, until the completion of cell cycle. The polyunsatd. fatty acids (PUPA) of n-3 family have been considered as authentic immunosuppressors; however, their mechanisms of action in T-cell activation have not been well elucidated. In this review, we will shed light on the intervention of n-3 PUFA with the second messenger cascade, initiated during early and late events of T-cell activation. We will particularly focus on how these fatty acids can modulate the. Prodn. of diacylglycerol and the activation of **protein kinase C** (PKC), mitogen activated protein (MAP) kinase, calcium signalling and translocation of transcriptional factors, implicated in the regulation of gene transcription in T-cells.

REFERENCE COUNT: 126 THERE ARE 126 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

However, in mice and rats one can follow the generation of secretory APP products but the detection of rodent .beta.-amyloid peptides is delicate. Therefore, we adapted the MAM model to guinea pigs, which have a human .beta.-amyloid sequence, and investigated the relation between secretory APP processing and .beta.-amyloid generation in vivo. In the brains of microencephalic guinea pigs we obsd. increased levels of secretory APP fragments but no change in the concn. of .beta.-amyloid peptides. Our results indicate that both pathways of APP processing are differentially controlled under these exptl. conditions in vivo.

REFERENCE COUNT: 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:279220 CAPLUS
DOCUMENT NUMBER: 138:383626
TITLE: Innate immune signaling during phagocytosis
AUTHOR(S): Underhill, David M.
CORPORATE SOURCE: The Institute for Systems Biology, Seattle, WA, USA
SOURCE: Innate Immunity (**2003**), 341-359. Editor(s): Ezekowitz, R. Alan B.; Hoffmann, Jules A. Humana Press Inc.: Totowa, N. J.
CODEN: 69DSYS; ISBN: 1-58829-046-8
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: **English**

AB A review discusses the innate immune phagocytic receptors, the mechanisms by which these receptors trigger particle internalization, and the spatial, temporal, and functional relation between particle internalization and the nature of the accompanying inflammatory response. Phagocytosis requires activation of complex signaling networks that develop over time to mediate internalization of pathogens and proinflammatory signaling also requires activation of complex signaling networks that det. the nature of the cellular response. These two processes are intrinsically linked in space and time and use many of the same signaling components.

REFERENCE COUNT: 108 THERE ARE 108 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:267689 CAPLUS
DOCUMENT NUMBER: 139:19689
TITLE: Ca2+ regulation of Drosophila phototransduction
AUTHOR(S): O'Tousa, Joseph E.
CORPORATE SOURCE: Department of Biological Sciences, University of Notre Dame, Notre Dame, IN, 46556, USA
SOURCE: Advances in Experimental Medicine and Biology (**2002**), 514(Photoreceptors and Calcium), 493-505
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**

AB A review. Drosophila vision research has benefited from simultaneous application of genetic, mol., electrophysiol. analyses. The work establishes an essential role of Ca2+ in regulation of phototransduction. Many different proteins are the targets of Ca2+ regulation and these proteins act at multiple steps of the process. These targets include proteins involved in the rhodopsin cycle, proteins responsible for intermediate steps of phototransduction, and the TRP and TRPL light-gated channels. The regulation of these phototransduction components by Ca2+ occurs in 3 different ways. First, the presence of Ca2+/calmodulin-binding sites in phototransduction-mediating proteins places these proteins under Ca2+ control. Second, a **protein kinase**

**C** regulated by Ca2+ phosphorylates proteins to modulate their activity. Finally, some proteins contain Ca2+-binding sites and apparently are directly regulated by Ca2+. Here I review the photoreceptor proteins regulated by Ca2+, and summarize current views on the roles of these proteins in the Drosophila photoresponse.
REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:267620 CAPLUS
DOCUMENT NUMBER: 139:16988
TITLE: Ruboxistaurin, Eli Lilly
AUTHOR(S): Wheeler, Glen D.
CORPORATE SOURCE: Vancouver, BC, V5Z 1V1, Can.
SOURCE: IDrugs (**2003**), 6(2), 159-163
CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**
AB A review. Eli Lilly & Co is developing the **protein kinase C**-.beta. inhibitor ruboxistaurin, the lead compd. from a series of 14-membered macrocycles, for the potential treatment of diabetic retinopathy, diabetic peripheral neuropathy and macular edema.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

CODEN: IMRED2; ISSN: 0105-2896
PUBLISHER: Blackwell Munksgaard
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**

AB A review. The distinct **protein kinase C** (PKC) multigene family (PKC gene module) is known to be the 'classic' intracellular receptor for mitogenic phorbol esters, and it is widely accepted in the scientific community that the 'PKC effect' is essential in activation, differentiation, adhesion and motility, as well as in cellular survival, of T cells. Nevertheless, the first concepts about PKC isotype heterogeneity of cellular localization and function emerged only recently, when the PKC-.vtheta. pathways were mapped to crit. signaling networks that control T cell receptor (TCR)/CD3-dependent interleukin (IL)-2 prodn. and proliferation in T lymphocytes. This review summarizes the current knowledge about T cell expressed PKC gene products, their known and/or suspected regulation and cellular effector pathways, as well as physiol. functions in T lymphocytes (as detd. by mol. cell biol. and ongoing mouse genetic studies). Given PKCs integral role in T cell function but today's very fragmentary mol. understanding of directly PKC-mediated effector functions in transmembrane signaling, a 'mol. biosystematics' approach is suggested to resolve the isotype-selective functions of this PKC gene family. Such an approach has to be based not only on genomic/cytogenetic anal. to establish its genetic relationships but also on biochem./cell biol. and genetic studies to resolve its functional diversity and, ultimately, nonredundant roles in real T cell physiol.

REFERENCE COUNT: 113 THERE ARE 113 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:347452 CAPLUS
DOCUMENT NUMBER: 138:383657
TITLE: **Protein kinase C** -.vtheta. (PKC.vtheta.): it's all about location, location, location
AUTHOR(S): Altman, Amnon; Villalba, Martin
CORPORATE SOURCE: Division of Cell Biology, La Jolla Institute for Allergy and Immunology, San Diego, CA, USA
SOURCE: Immunological Reviews (**2003**), 192, 53-63
CODEN: IMRED2; ISSN: 0105-2896
PUBLISHER: Blackwell Munksgaard
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**

AB A review. Much progress has been made in understanding the function of **protein kinase C**-.vtheta. (PKC.vtheta.) in the immune system since this Ca2+-independent PKC isotype was isolated in 1993 as an enzyme that is highly expressed in T lymphocytes and in muscle cells. Biochem. and genetic approaches revealed that, while dispensable for T-cell development, PKC.vtheta. is required for the activation of mature T cells and for interleukin (IL)-2 prodn. This deficiency results from impaired receptor-induced stimulation of the transcription factors AP-1 and NF-.vkappa.B. PKC.vtheta. integrates T-cell receptor (TCR)/CD28 costimulatory signals, which are essential for productive T-cell activation and, most likely, for prevention of T-cell anergy. A unique property of PKC.vtheta. is its highly selective recruitment to the central supramol. activation complex (cSMAC) region of the immunol. synapse (IS) in antigen-stimulated T cells. Our work revealed that this highly selective localization is not entirely dependent on phospholipase C (PLC) activity and diacylglycerol (DAG) prodn. Instead, a novel signaling pathway that requires functional Vav1, phosphatidylinositol 3-kinase (PI3-K), the small GTPase Rac and actin cytoskeleton reorganization regulates the localization and, perhaps, activation of PKC.vtheta.. PKC.vtheta. also provides a survival signal, which protects T cells from apoptosis. Addnl. work is required to identify the immediate targets of

FSH.beta. subunit as well. Like those of the mammalian counterparts, the coho salmon LH.beta. gene promoter is driven by a strong proximal tripartite element to which three different transcription factors bind. These include Sf-1 and Pitx-1 as in mammals, but the function of the Egr-1 appears to have been replaced by the estrogen receptor (ER). The GnRH responsive region in tilapia FSH.beta. 5' flanking region spans the canonical AP1 and CRE motifs implicating both elements in conferring GnRH responsiveness. Generally, high levels of gonadal steroids are assocd. with high LH.beta. transcript levels whereas those of FSH.beta. are reduced when pituitary cells are exposed to high steroid levels. Gonadal or hypophyseal activin also participate in the regulation of FSH.beta. and LH.beta. mRNA levels. However, gonadal effects are dependent on the gender and stage of maturity of the fish.

REFERENCE COUNT: 251 THERE ARE 251 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:347454 CAPLUS
DOCUMENT NUMBER: 138:383659
TITLE: Lipid phosphatases in the regulation of T cell activation: living up to their PTEN-tial
AUTHOR(S): Seminario, Maria-Cristina; Wange, Ronald L.
CORPORATE SOURCE: Laboratory of Cellular and Molecular Biology, National Institutes on Aging/IRP/NIH/DHHS, Baltimore, MD, USA
SOURCE: Immunological Reviews (**2003**), 192, 80-97
CODEN: IMRED2; ISSN: 0105-2896
PUBLISHER: Blackwell Munksgaard
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**

AB A review. The initiating events assocd. with T activation in response to stimulation of the T cell antigen receptor (TCR) and costimulatory receptors, such as CD28, are intimately assocd. with the enzymically catalyzed addn. of phosphate not only to key tyrosine, threonine and serine residues in proteins but also to the D3 position of the myo-inositol ring of phosphaddylinositol (PtdIns). This latter event is catalyzed by the lipid kinase phosphoinositide 3-kinase (PI3K). The consequent prodn. of PtdIns(3,4)P2 and PtdIns(3,4,5)P3 serves both to recruit signaling proteins to the plasma membrane and to induce activating conformational changes in proteins that contain specialized domains for the binding of these phospholipids. The TCR signaling proteins that are subject to regulation by PICK include Akt, phospholipase C.gamma.1 (PLC.gamma.1), **protein kinase C**.zeta. (PKC-.zeta.), Itk, Tec and Vav, all of which play crit. roles in T cell activation. As is the case for phosphorylation of protein substrates, the phosphorylation of PtdIns is under dynamic regulation, with the D3 phosphate being subject to hydrolysis by the 3-phosphatase PTEN (phosphatase and tensin homolog deleted on chromosome 10), thereby placing PTEN in direct opposition to PI3K. In this review we consider recent data concerning how PTEN may act in regulating the process of T cell activation.

REFERENCE COUNT: 198 THERE ARE 198 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:347453 CAPLUS
DOCUMENT NUMBER: 138:383658
TITLE: The PKC gene module: molecular biosystematics to resolve its T cell functions
AUTHOR(S): Baier, Gottfried
CORPORATE SOURCE: Institute of Medical Biology and Human Genetics, University of Innsbruck, Austria
SOURCE: Immunological Reviews (**2003**), 192, 64-79

L3 ANSWER 1 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:446565 CAPLUS
TITLE: NF-Fk signaling: an alternate pathway for oxidative stress response
AUTHOR(S): Storz, Peter; Toker, Alex
CORPORATE SOURCE: Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 02215, USA
SOURCE: Cell Cycle (**2003**), 2(1), 9-10
CODEN: CCEYAS; ISSN: 1538-4101
PUBLISHER: Landes Bioscience
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**
AB A new signalling pathway that mediates NF-FkB-dependent responses induced by oxidative stress is described. In this pathway, stimulation of cells with reactive oxygen species (H2O2) leads to the activation of the tyrosine kinases pp60-Src and c-Abl, and one consequence of this is the tyrosine phosphorylation and activation of the serine/threonine protein kinase (PKD). PKD is distantly related to the **protein kinase C** family, and is activated in response to numerous extracellular stimuli, including hydrogen peroxide. Oxidative stress-induced PKD activation leasd to NF-FkB activation via the classical IKK complex activation pathway. Signaling through Src-Abl-PKD-IKK-NF-FkB pathway leads to enhanced protection from oxidative-stress induced cell death. The pathway represents essential mechanism which cells utilize to respond to the adverse environment of oxidative stress, and effective;ly increase their survival ability.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 678 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:379417 CAPLUS
TITLE: Regulation of fish gonadotropins
AUTHOR(S): Yaron, Zvi; Gur, Gal; Melamed, Philippa; Rosenfeld, Hanna; Elizur, Abigail; Levavi-Sivan, Berta
CORPORATE SOURCE: Department of Zoology and Norman and Rose Lederer Chair of Experimental Biology, Tel-Aviv University, Tel Aviv-Jaffa, 69978, Israel
SOURCE: International Review of Cytology (**2003**), 225, 131-185
CODEN: IRCYAJ; ISSN: 0074-7696
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: **English**
AB A review. Neurohormones similar to those of mammals are carried in fish by hypothalamic nerve fibers to regulate directly FSH (FSH) and LH (LH). Gonadotropin-releasing hormone (GnRH) stimulates the secretion of FSH and LH and the expression of the glycoprotein hormone .alpha. (GP.alpha.), FSH.beta., and LH.beta., as well as their secretion. Its signal transduction leading to LH release is similar to that in mammals although the involvement of cAMP-protein kinase A (cAMP-PKA) cannot be ruled out. Dopamine (DA) acting through DA D2 type receptors may inhibit LH release, but not that of FSH, at sites distal to activation of **protein kinase C** (PKC) and PKA. GnRH increases the steady-state levels of GP.alpha., LH.beta., and FSH.beta. mRNAs. Pituitary adenylate cyclase-activating polypeptide (PACAP) 38 and neuropeptide Y (NPY) potentiate GnRH effect on gonadotropic cells, and also act directly on the pituitary cells. Whereas PACAP increases all three subunit mRNAs, NPY has no effect on that of FSH.beta.. The effect of these peptides on the expression of the gonadotropin subunit genes is transduced differentially; GnRH regulates GP.alpha. and LH.beta. via PKC-ERK and PKA-ERK cascades, while affecting the FSH.beta. transcript through a PKA-dependent but ERK-independent cascade. The signals of both NPY and PACAP are transduced via PKC and PKA, each converging at the ERK level. NPY regulates only GP.alpha.- and LH.beta.-subunit genes whereas PACAP regulates the

Revised Interim Written Description Guideline Training Materials

# SYNOPSIS OF APPLICATION OF WRITTEN DESCRIPTION GUIDELINES

## Contents

## SYNOPSIS OF APPLICATION OF WRITTEN DESCRIPTION GUIDELINES

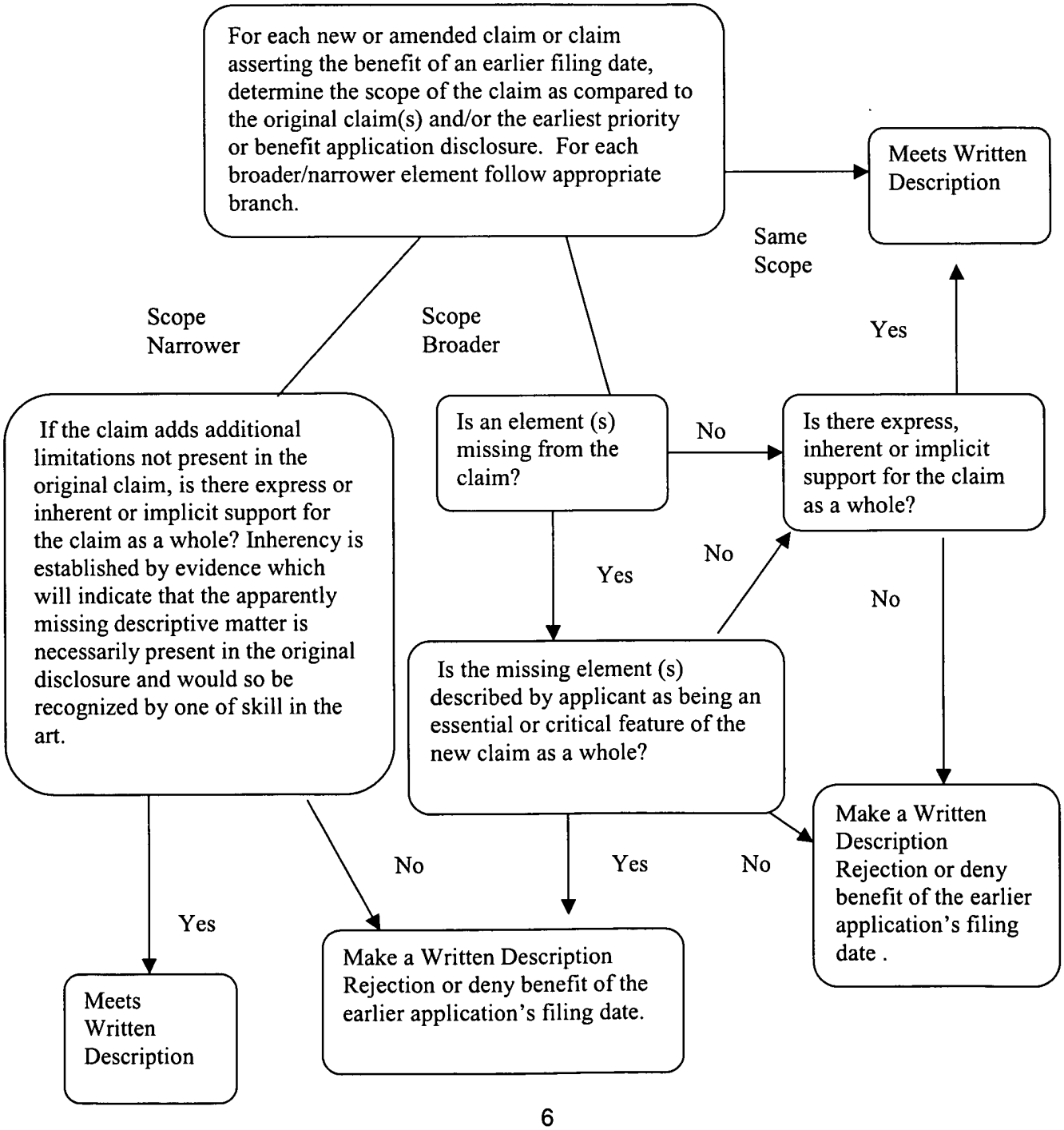
It is assumed at this point in the analysis that the specification has been reviewed and an appropriate search of the claimed subject matter has been conducted. It is also assumed that the examiner has identified which features of the claimed invention are conventional taking into account the body of existing prior art. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. If the examiner determines that the application does not comply with the written description requirement, the examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. It should also be noted that the test for an adequate written description is separate and distinct from the test under the enablement criteria of 35 U.S.C. § 112 first paragraph. The absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. 112, para. 1, for lack of adequate written description. Limitations may not, however, be imported into the claims from the specification.

The following examples only describe how to determine whether the written description requirement of 35 U.S.C. 112, para. 1 is satisfied. Regardless of

the outcome of that determination, Office personnel must complete the patentability determination under all the relevant statutory provisions of Title 35 of the U.S. Code. Once Office personnel have concluded analysis of the claimed invention under all the statutory provisions, including 35 U.S.C. 101, 112, 102, and 103, they should review all the proposed rejections and their bases to confirm their correctness. Only then should any rejection be imposed in an Office action. The Office action should clearly communicate the findings, conclusions, and reasons which support them. When possible, the Office action should offer helpful suggestions on how to overcome rejections.

# Written Description Amended or New Claims, or Claims Asserting the Benefit of an Earlier Filing Date

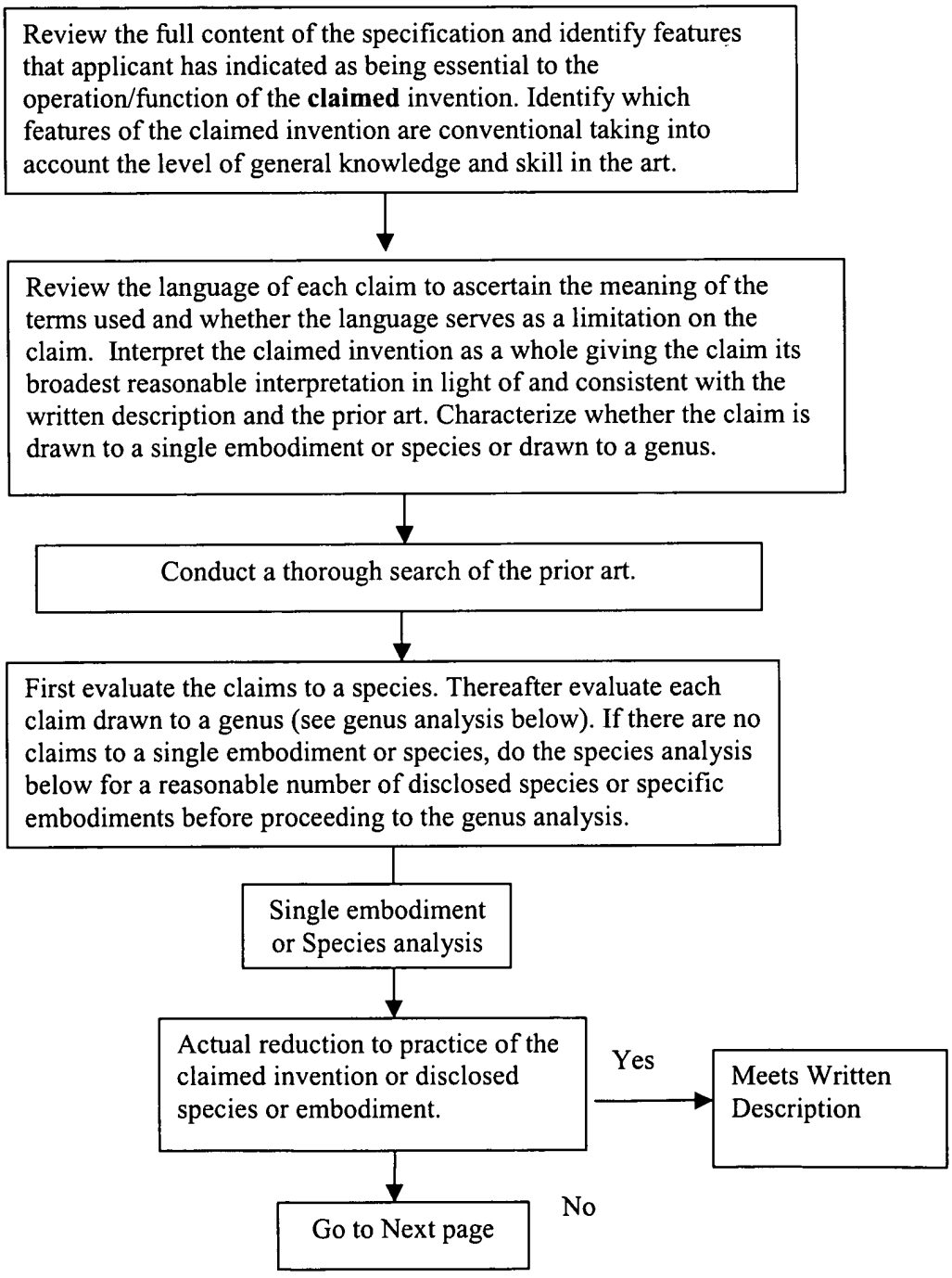
## Decision Tree



## Written Description

## Original Claims

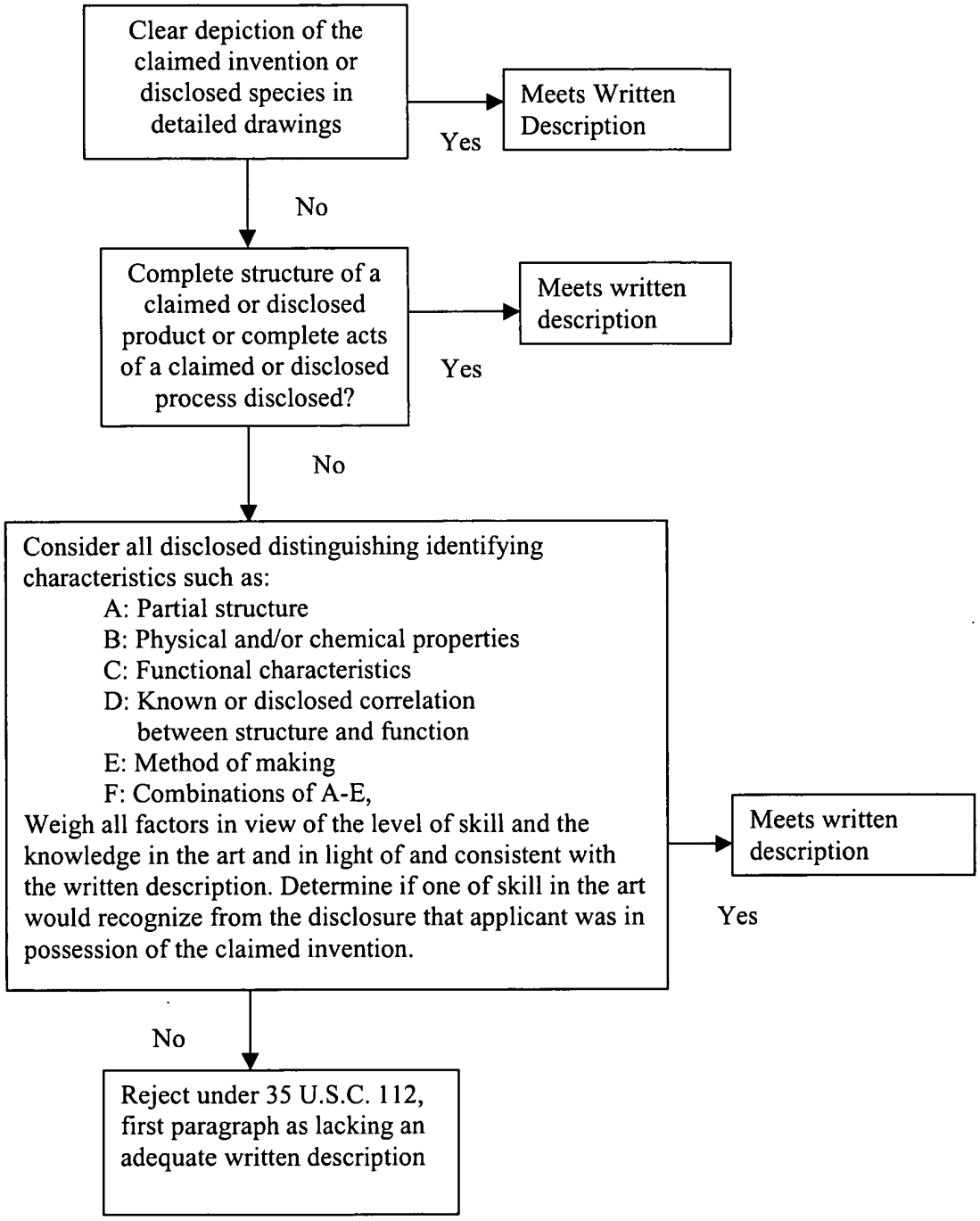
## --Decision Tree--



**Written Description**

**Original Claims**

**--Decision Tree--**

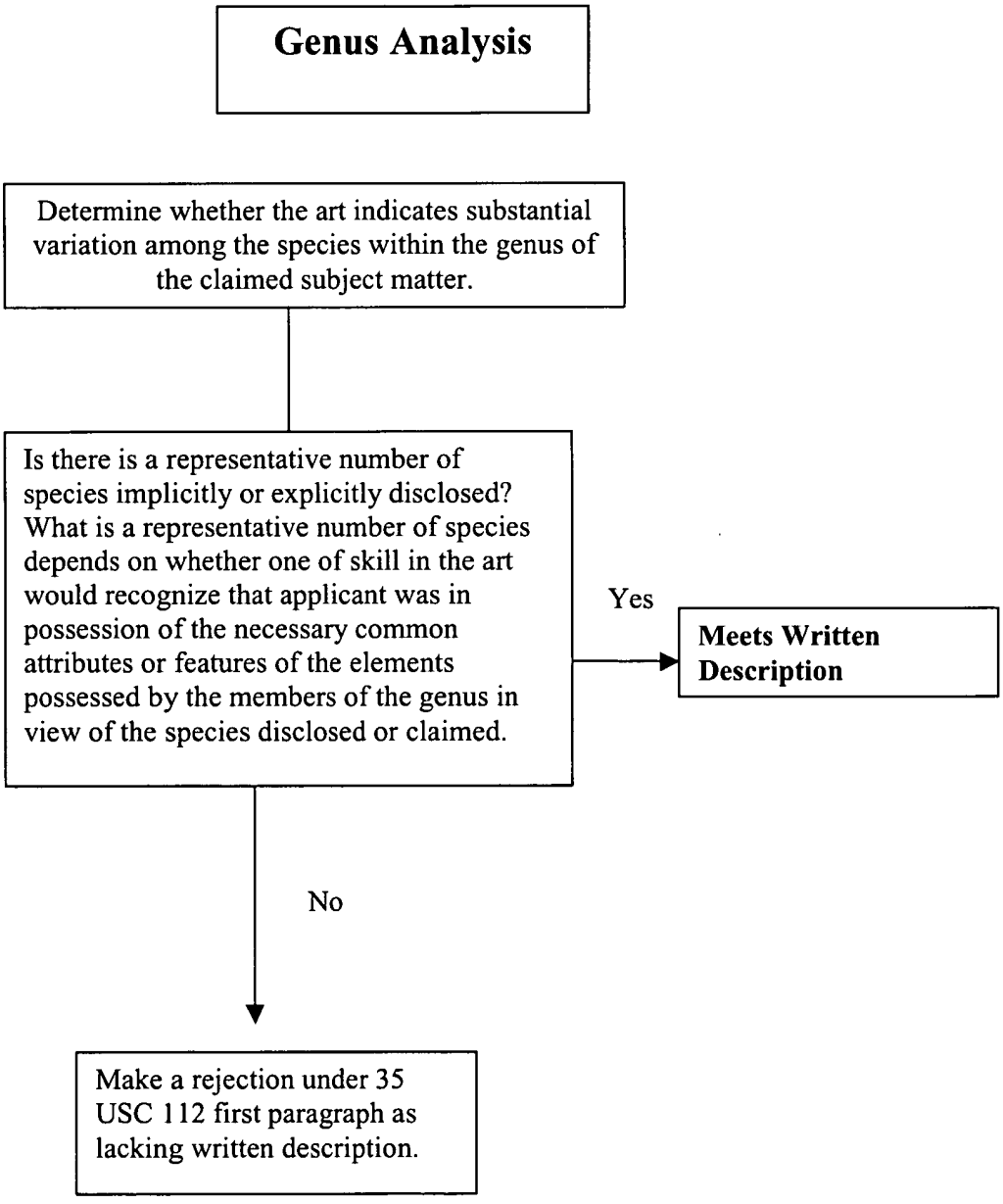


**Written Description**

**Original Claims**

**Decision Tree**

**--Page 3--**



## WRITTEN DESCRIPTION TRAINING EXAMPLES

**Example 1: Amended claims**

**Fact Pattern:**

The specification is directed to a sectional sofa with a console between two reclining chairs, wherein control means for the reclining chairs are mounted on the console. The original disclosure clearly identifies the console as the only possible location for the controls, and provides for only the most minor variation in the location of the controls, e.g., the controls may be mounted on the top or side surfaces of the console or on the front wall. Additionally, the specification states that the purpose for the console is to house the controls. The original claims required the control elements to be present in the console. Applicant subsequently amends the claims to remove this limitation.

**Amended Claim:**

1. (Amended) A sectional sofa comprising:

a pair of reclining seats disposed in parallel relationship with one another in a double reclining seat sofa section, said double reclining seat sofa section being without an arm at one end whereby a second sofa section of the sectional sofa can be placed in abutting relationship with the end of the double reclining seat sofa section without an arm so as to form a continuation thereof,

each of said reclining seats having a backrest and seat cushion and movable between upright and reclined positions, said backrests and seat cushions of the pair of reclining sets lying in respective common planes when the seats are in the same positions,

a fixed console disposed in the double reclining seat sofa section between the pair of reclining seats and with the console and reclining seats together comprising a unitary structure, said console including an armrest portion for each of the reclining seats, said arm rests remaining fixed when the reclining seats move from one to another of their positions, and

**a pair of control means [located upon the center console to enable each of the pair of reclining seats to move separately between the reclined and upright positions] mounted on the double reclining seat sofa section and each readily accessible to an occupant of its respective reclining seat and when actuated causing the respective reclining seat to move from the upright to the reclined position.**

**Analysis:**

The amended claim is broader than the original claim in that the pair of control means is no longer required to be located on the center console. Thus, control means mounted on a center console is an element missing from the claim. The specification describes the location of the control means on the console as an essential feature of the claimed invention as a whole because the specification clearly identifies the console as the only possible location for the controls, and states that the purpose for the console is to house the controls.

**Conclusion:**

Reject the amended claim under 35 USC §112 first paragraph as lacking adequate written description.

**Example 2: 35 USC 120 Priority**

**Fact Pattern:**

The specification is directed to artificial hip sockets that include cup implants adapted for insertion into an acetabular, or hip, bone. The specification indicates that the shape of the cup is not important, as long as the implant can effectively function as an artificial hip socket. The application is a continuation in part of a parent application that describes an acetabular cup prosthesis wherein the cup is a trapezoid, a truncated cone, or of conical shape. All of these terms describe a conical cup. The parent specification also touts the criticality of a conical cup over all other shape cups.

A reference disclosing the claimed invention published between the filing date of the parent application and the instant application. Applicant asserts entitlement to the filing date of the parent application.

**Claim:**

1. An acetabular cup prosthesis comprising (1) a body extending generally longitudinally and terminating into front and rear surfaces, said front surface extending substantially transversely to said body; and (2) at least one fin for securing said cup to a prepared acetabulum cavity, said fin having a length extending generally longitudinally from said front surface toward said rear surface continuously along said body throughout the entire length of said fin, and said fin being configured so as to extend radially outwardly beyond the perimeter of said front surface and said body so as to engage with the cavity thereby securing said cup.

2. The prosthesis of claim 1, wherein the body has a generally conical outer surface.

**Analysis:**

Claim 1 in the instant application is directed to an acetabular cup prosthesis wherein the shape of the cup is not specifically defined (see element (1) of claim 1). The claim is broader than the disclosure in the parent application, which only describes a conical cup. Claim 1 is missing the element of a conical shape. This element is an essential or critical feature of the invention described in the parent application because the parent application only discloses a conical shape and the conical shape is described as critical over other shapes.

Claim 2 of the instant application is directed to an acetabular cup prosthesis wherein the cup has a generally conical outer surface. The claim is of the same scope as the invention described in the parent application.

**Conclusion:**

Reject claim 1 over the prior art reference, and indicate that the claim is not entitled to the benefit of the earlier application filing date.

Indicate that claim 2 is entitled to the benefit of the parent application filing date.

Note that if applicant had added the subject matter of claim 1 of this application to the parent application in an amendment, the claim would have been rejected under 35 U.S.C. 112, first paragraph as lacking an adequate written description.

**Example 2A: Essential element missing from original claim**

**Fact Pattern:**

The fact situation of example 2 above is similar to the fact situation of the instant example, however, there is no parent application in this example.

The specification is directed to artificial hip sockets that include cup implants adapted for insertion into an acetabular, or hip, bone. The specification indicates that the shape of the cup is critical to permit the implant to effectively function as an artificial hip socket. The application describes an acetabular cup prosthesis wherein the cup is a trapezoid, a truncated cone, or of conical shape. All of these terms describe a conical cup. The specification also touts the criticality of a conical cup.

**Claims:** Same as claims 1 and 2 of example 2 above.

**Analysis:**

Claim 1 in the instant application is directed to an acetabular cup prosthesis wherein the shape of the cup is not specifically defined (see element (1) of claim 1). The claim is broader than the disclosure in the instant application that only describes a conical cup. Claim 1 is missing the element of a conical shape. A review of the specification indicates that a cup implant having a shape which can effectively function as an artifical hip socket is critical to the operation/function of the claimed invention. The application discloses a conical shape cup and the conical shape is described as critical over other shapes. The specification indicates that the invention **as claimed** will not function in its intended manner without the specific cup

shape. Therefore this element is essential to the function/operation of the invention.

Claim 1 is directed to a genus. There is no actual reduction to practice or clear depiction of the claimed invention in detailed drawings; however, the complete structure of a species of the claimed prosthesis (with conical shape) is disclosed. The disclosed species is not representative of the genus because the specification indicates that without the conical shape the invention will not operate as intended. Therefore, applicant was not in possession of the necessary common attributes of the elements possessed by the members of the genus. A written description rejection should be made in this situation.

**Example 2B: A preferred element missing from original claim**

**Fact Pattern:**

The fact situation of example 2B is similar to example 2A above except that in this example the shape of the conical cup is described as being preferred.

The specification is directed to artificial hip sockets that include cup implants adapted for insertion into an acetabular, or hip, bone. The specification indicates that the shape of the cup must permit the implant to effectively function as an artificial hip socket. The application describes an acetabular cup prosthesis wherein the cup is preferably a trapezoid, a truncated cone, or of conical shape. All of these terms describe a conical cup. The specification emphasizes that a conical cup is the preferred embodiment.

**Claims:** Same as claims 1 and 2 of example 2 above.

**Analysis:**

Claim 1 in the instant application is directed to an acetabular cup prosthesis wherein the shape of the cup is not specifically defined (see element (1) of claim 1). The claim is broader than the disclosure in the instant application that only describes a conical cup. Claim 1 is missing the element of a conical shape. A review of the specification indicates that a cup implant having a conical shape is preferred but has no apparent bearing to the operation/function of the claimed invention. Therefore this element is not essential to the function or operation of the invention.

Claim 1 is directed to a genus. Although there is no actual reduction to practice or clear depiction of the claimed invention in detailed drawings, the complete structure of a species of the claimed prosthesis (with conical shape) is disclosed. The disclosed species is representative of the genus because there is a known correlation between the structure and the function of claimed invention and one of skill in the art would recognize that applicant was in possession of the necessary common attributes of the elements possessed by the members of the genus. The invention as claimed will function in its intended manner even without the specific cup shape. No written description rejection should be made in this situation.

**Note:** ***If the specification needs to be amended to be consistent with an original claim, see MPEP 608.01(o).***

**Example 3: New claims**

**Fact Pattern:**

The specification describes a form of computer technology called multi-threading. In essence, computers with multi-threading capabilities can switch between tasks with such rapidity that they appear to be performing two or more tasks at once. The specification describes one illustrative example in the specification wherein one of the program threads is an editor and another thread is a code processing routine in the form of a compiler. As the operator strikes keys at the keyboard, the compiler thread executes between each successive pair of keystrokes to process the entered source code concurrently with the editing operation. By the time the operator has finished entering or editing the code the compiler thread will have completed most of the required processing, thereby freeing the operator from lengthy periods of waiting for extensive code processing.

In this illustrative embodiment the interrupt operation of the central processor is periodically activated by a timer or clock. Each interrupt operation asynchronously preempts the executing compiler thread and passes control of the central processor to an interrupt service routine. The input port is then polled to test if a key has been struck at the keyboard. If not, the interrupt is terminated and control returns to the compiler thread. If polling the port reveals that a key has been struck then the interrupt service routine invokes the editor thread which takes control of the central processor to perform a character code entry or other edit operation. In addition to the description above, the application's abstract references an editor, compiler, interrupt means, and return means, and the "Object of the Invention" section

and the "Description of Prior Art" clearly discuss the importance of an editor and compiler.

The original claims required, *inter alia*, an editor, a compiler, an interrupt means and a return means. These elements are missing from new claim 20.

**Claim:**

20. A computer-readable disk memory having a surface formed with a plurality of binary patterns constituting a multithreaded application program executable by a desktop computer having a central microprocessor, a memory, means for loading said application program into a defined address space of said memory, and a clock-driven periodically-activated interrupt operation, said multithreaded program comprising

a plurality of sets of instructions with each set executable by said microprocessor,

a first of said sets of instructions executable to provide a first thread of execution having control of the central microprocessor,

said first thread of execution being periodically preempted in response to activations of an interrupt operation at predetermined fixed time intervals, and

a second of said sets of instructions executable to provide a second thread of execution to acquire control of the central microprocessor,

each of said threads having direct access to said program memory address space so as to provide fast efficient preemption of one thread by

another thread and switching of control of the central microprocessor back and forth among the threads at a rate so rapid that the threads execute effectively simultaneously.

**Analysis:**

Claim 20 is a new claim, which is broader in scope than the original claims. There are four elements missing from the claims (the editor, compiler, interrupt means, and return means). These missing elements are described by applicant as being an essential or critical feature of the claimed invention as a whole as evidenced by applicant's repeated reliance on the presence of these elements throughout the originally filed disclosure. Multiple sections within the application make clear that these four elements served integral functions in the overall invention.

**Conclusion:**

Reject claim 20 as lacking an adequate written description because four elements described as essential or critical are omitted. The omitted elements are: editor, compiler, interrupt means, and return means.

**Example 4 : <u>Original claim</u>**

**Fact Pattern:**

The invention is directed to a form of autopilot, described as a "heading lock," which enables a person to maintain directional control over a watercraft without constant manipulation of trolling motor controls. The preferred embodiment, as set forth in the written description and clearly depicted in detailed drawings, employs a compass mounted to the head of the "heading lock" unit, which monitors the direction of the thrust motor. The heading lock is coupled to the trolling motor; in a preferred embodiment, the heading lock is mechanically coupled to the trolling motor. The disclosure specifically notes that the direction of the thrust motor is considered to be the same as the direction of the boat since the trolling motor is mounted on the bow of the boat. The specification indicates that the electronic steering system continues to monitor the current heading of the thrust and also indicates that the heading detector continuously monitors the current heading of the boat. The term "heading" is used interchangeably throughout the written description to refer to both the direction of the trolling motor and the direction of the boat.

**Claim:**

1. A heading lock coupled to a trolling motor producing a thrust disposed to pull a watercraft, said heading lock comprising:

a steering motor coupled to said trolling motor, said steering motor being disposed to affect the orientation of said trolling motor in response to input signals;

a steering circuit electrically coupled to said steering motor, said steering circuit being disposed to generate said input signals to said steering motor in response to heading signals; and

a heading detector electrically coupled to said steering circuit, said heading detector being disposed to transmit said heading signals to said steering circuit.

**Analysis:**

Applicant has identified a heading lock comprising a steering system coupled to a trolling motor and a heading detector, as features essential to the operation of the claimed invention. Although the heading lock is preferably mechanically coupled to the trolling motor, the applicant does not describe the type of coupling as essential to the claimed invention as a whole. A search of the prior art shows that various means for coupling a heading lock to a trolling motor are conventional in the art. The claim is drawn to a single embodiment. Although there is no reduction to practice of the claimed invention, the claimed invention is clearly depicted in detailed drawings.

**Conclusion:**

The claim is adequately described.

**Example 5: Flow Diagrams**

**Fact Pattern:**

The specification is directed to a mechanism for controlling the mode of operation of a modem. A modem is used for modulating and demodulating signals, both analog and digital, over telephone lines. It has two modes: (1) a transparent mode, in which the modem performs the modulation-demodulation function, and (2) a command mode, in which the modem responds to predetermined commands and performs operations by executing a set of instructions stored in Read-Only-Memory (ROM) or firmware. An escape command tells the modem when to switch between transparent and command modes.

The application claims an improved mechanism for detecting an escape command by a modem. The decision making capability and timing means preferably reside in a microprocessor, preferably a Z-8 type microprocessor. The specification discloses logic flow diagrams and provides a detailed functional recitation that describes how to program computers to detect an escape command, but the specification does not provide a computer program listing with source code. The specification describes the escape sequence as one full second of no data, followed by the predetermined escape command, followed by another full second of no data.

**Claim:**

1. In a modem including a data input port for connecting said modem to a utilization device, and a telephone port for connecting said modem to a

telephone line, said modem being of the type having two distinct modes of operation:

(a) a transparent mode of operation for which said modem provides modulated signals to said telephone port in response to data signals provided to said data input port; and

(b) a command mode of operation for which said modem responds to said data signals provided to said data input port as instructions to said modem;

said modem including means defining a predetermined sequence of said data signals as an escape character; the improvement comprising:

timing means for detecting each occurrence of a passage of a predetermined period of time after provision of one of said data signals to said data input port; and

means, operative when said modem is in said transparent mode of operation, for detecting provision of said predetermined sequence of said data signals, and for causing said modem to switch to said command mode of operation, if and only if said predetermined sequence of data signals occurs contiguous in time with at least one said occurrence of said passage of said predetermined period of time during which none of said data signals are provided to said data input port.

**Analysis:**

After a review of the full content of the specification, the examiner finds that a modem having two modes of operation (transparent and

command), a timing means, and a means for detecting an escape sequence and causing the modem to switch from the transparent to the command mode are essential to the operation and function of the claimed invention. The specification does not describe a particular timing means or means for detecting the escape command and switching to the command mode. The claim is drawn to a genus. A search of the prior art indicates that the structure of the hardware required is conventional, and that one skilled in the art would know how to program a microprocessor to perform the necessary steps described in the specification. A review of the art indicates that there is no substantial variation among the species within the genus. Although no embodiments have been actually reduced to practice, a review of the specification shows that the claimed invention has been reduced to drawings in view of the detailed functional flow diagrams. Since the claimed invention is supported by conventional hardware structure and because there is a functional description of what the software does to operate the computer, there is sufficient description of the claimed invention. Disclosing a microprocessor capable of performing certain functions is sufficient to satisfy the requirement of section 112, first paragraph, when one skilled in the relevant art would understand what is intended and know how to carry it out.

**Conclusion:**

The claimed invention has been adequately described.

## Biotechnology Examples

### Example 6: Genes

**Specification:** The specification describes an isolated cDNA fragment (SEQ ID NO: 1; a 100mer) obtained from a human glioblastoma cDNA library. SEQ ID NO: 1 is asserted to be homologous to a known DNA molecule that encodes the extracellular domain of a glial specific G-coupled protein receptor whose function is associated with glial cell differentiation. The observed homology is sufficient to support a conclusion that SEQ ID NO: 1 would be glial specific. Further, it would be reasonable to infer that a G-coupled protein receptor encoded by a cDNA that comprised SEQ ID NO: 1 would be involved in the regulation of glial cell differentiation. In the description, applicant defines a "gene" as including naturally occurring regulatory elements and untranslated regions necessary and sufficient to mediate the expression of a cDNA comprising SEQ ID NO: 1. The specification describes methods for cloning nucleic acids that encode full-length glial specific G coupled protein receptors. The specification also discloses that SEQ ID NO: 1 can be used as a probe for identifying the presence of nucleic acids encoding glial specific G-coupled protein receptors in mammals. Glial specific G-coupled protein receptors are disclosed as useful in drug discovery methods to identify agents that regulate glial differentiation. The specification defines a probe as consisting of SEQ ID NO: 1 and between five to 10 additional nucleotides on either end of SEQ ID NO: 1.

**Claim:**

An isolated gene comprising SEQ ID NO: 1.

**Analysis:**

A review of the specification indicates that elements which are not particularly described, including regulatory elements and untranslated regions, are essential to the function of the claimed invention because applicant's definition of "gene" requires them. Additionally, SEQ ID NO: 1 is disclosed as being essential to the function of the claimed invention. The art indicates that the structure of genes with naturally occurring regulatory elements and untranslated regions is empirically determined. For example, the structural elements of "gene" mediating the expression of a particular protein in the liver may be different than the structural elements of the "gene" mediating the expression of the same protein in the brain. Therefore the structure of these elements which applicant considers as being essential to the function of the claim are not conventional in the art.

The claim is drawn to a genus, i.e., any gene which comprises SEQ ID NO: 1.

A search of the prior art indicates that SEQ ID NO: 1 is otherwise novel and unobvious, and no associated genomic clones have been identified.

There is no actual reduction to practice of the claimed invention, clear depiction of the claimed invention in the drawings or complete detailed description of the structure.

Considering all disclosed distinguishing identifying characteristics, there is a disclosure of partial structure (SEQ ID NO: 1) as well as the function of the gene as coding for a G-coupled protein receptor.

However, there is no known or disclosed correlation between this function and the structure of the non-described regulatory elements and untranslated regions of the gene. Furthermore, there is no additional disclosure of physical and/or chemical properties. Weighing all factors in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of genes which comprise SEQ ID NO: 1.

**Conclusion:**

Reject claim 1 under 35 USC 112 first paragraph as lacking an adequate written description. The examiner should make a rejection following a similar type of reasoning as that set forth above.

**Note: Applicant may overcome this rejection by claiming a probe which consists essentially of SEQ ID NO: 1, since the specification teaches that a probe can have no more than 10 additional nucleic acid residues at either end of the molecule. The examiner should make an express determination that "consisting essentially of" admits of no more than 10 additional residues at either end of the molecule.**

**Example 7: EST**

**Specification:** The specification discloses SEQ ID NO: 16 which is a partial cDNA. The specification does not address whether the cDNA crosses an exon/intron splice junction. The specification discloses that this sequence will specifically hybridize with the complement of the coding sequence of a gene of an infectious yeast. The presence of the nucleic acid detected by hybridization with the complement of the coding sequence is useful for identifying yeast infections. Example 1 of the specification describes an experiment where SEQ ID NO: 16 was determined following characterization of a cDNA clone isolated from a cDNA library.

**Claim:**

An isolated DNA comprising SEQ ID NO: 16.

**Analysis:**

A review of the full content of the specification indicates SEQ ID NO: 16 is essential to the operation and function of the claimed invention. The specification indicates that the presence of DNA that hybridizes with SEQ ID NO: 16 is indicative of a yeast infection.

A review of the language of the claim indicates that the claim is drawn to a genus, i.e., any nucleic acid that minimally contains SEQ ID NO: 16 within it including any full length gene which contains the sequence, any fusion constructs or cDNAs.

The search indicates that SEQ ID NO: 16 is a novel and unobvious sequence.

There is a single species explicitly disclosed (a molecule consisting of SEQ ID NO: 16 that is within the scope of the claimed genus).

There is actual reduction to practice of the disclosed species.

The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. The present claim encompasses full-length genes and cDNAs that are not further described. There is substantial variability among the species of DNAs encompassed within the scope of the claims because SEQ ID NO: 16 is only a fragment of any full-length gene or cDNA species. When reviewing a claim that encompasses a widely varying genus, the examiner must evaluate any necessary common attributes or features. In the case of a partial cDNA sequence that is claimed with open language (comprising), the genus of, e.g., "A cDNA comprising [a partial sequence]," encompasses a variety of subgenera with widely varying attributes. For example, a cDNA's principle attribute would include its coding region. A partial cDNA that did not include a disclosure of any open reading frame (ORF) of which it would be a part, would not be representative of the genus of cDNAs because no information regarding the coding capacity of any cDNA molecule would be disclosed. Further, defining "the" cDNA in functional terms would not suffice in the absence of a disclosure of structural features or elements of a cDNA that would encode a protein having a stated function.

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a

substantial portion of the genus. Regents of the University of California v. Eli Lilly & Co., 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Here, the specification discloses only a single common structural feature shared by members of the claimed genus, i.e., SEQ ID NO: 16. Since the claimed genus encompasses genes yet to be discovered, DNA constructs that encode fusion proteins, etc., the disclosed structural feature does not "constitute a substantial portion" of the claimed genus. Therefore, the disclosure of SEQ ID NO: 16 does not provide an adequate description of the claimed genus.

Weighing all factors, 1) partial structure of the DNAs that comprise SEQ ID NO: 16, 2) the breadth of the claim as reading on genes yet to be discovered in addition to numerous fusion constructs and cDNAs, 3) the lack of correlation between the structure and the function of the genes and/or fusion constructs; in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of DNAs which comprise SEQ ID NO: 16.

**Conclusion:** The written description requirement is not satisfied.

**Caveat:** *In situations where the specification indicates that the SEQ ID NO: is a full-length cDNA open reading frame and the claim* ***cannot*** *read on a gene, the claimed invention would meet the written description requirement.*

**Example 8: <u>DNA fragment Encoding a Full Open Reading Frame (ORF)</u>**

**Specification:** The specification discloses that a cDNA library was prepared from human kidney epithelial cells and 5000 members of this library were sequenced and open reading frames were identified. The specification discloses a Table that indicates that one member of the library having SEQ ID NO: 2 has a high level of homology to a DNA ligase. The specification teaches that this complete ORF (SEQ ID NO: 2) encodes SEQ ID NO: 3. An alignment of SEQ ID NO: 3 with known amino acid sequences of DNA ligases indicates that there is a high level of sequence conservation between the various known ligases. The overall level of sequence similarity between SEQ ID NO: 3 and the consensus sequence of the known DNA ligases that are presented in the specification reveals a similarity score of 95%. A search of the prior art confirms that SEQ ID NO: 2 has high homology to DNA ligase encoding nucleic acids and that the next highest level of homology is to alpha-actin. However, the latter homology is only 50%. Based on the sequence homologies, the specification asserts that SEQ ID NO: 2 encodes a ligase.

**Claim 1:** An isolated and purified nucleic acid comprising SEQ ID NO: 2.

**Analysis:**

A review of the full content of the specification indicates SEQ ID NO: 2 is essential to the operation and function of the claimed invention. The specification indicates that SEQ ID NO: 2 encodes a protein that would be expected to act as a DNA ligase.

A review of the language of the claim indicates that the claim is drawn to a genus, i.e., any nucleic acid that minimally contains SEQ ID NO: 2. The claim is drawn to a nucleic acid comprising a full open reading frame. The claimed nucleic acid does not read on a genomic sequence because full-length mammalian cDNAs would not be expected to contain introns or transcriptional regulatory elements such as promoters that are found in genomic DNA. The claim reads on the claimed ORF in any construct or with additional nucleic acid residues placed at either end of the ORF.

The search indicates that SEQ ID NO: 2 is a novel and unobvious sequence.

There is a single species explicitly disclosed (a molecule consisting of SEQ ID NO: 2 that is within the scope of the claimed genus).

There is actual reduction to practice of the disclosed species.

One of skill in the art can readily envisage nucleic acid sequences which include SEQ ID NO: 2 because e.g. SEQ ID NO: 2 can be readily embedded in known vectors. Although there may be substantial variability among the species of DNAs encompassed within the scope of the claim because SEQ ID NO: 2 may be combined with sequences known in the art,

e.g. expression vectors, the necessary common attribute is the ORF (SEQ ID NO: 2).

Weighing all factors including (1) that the full length ORF (SEQ ID NO: 2) is disclosed and (2) that any substantial variability within the genus arises due to addition of elements that are not part of the inventor's particular contribution, taken in view of the level of knowledge and skill in the art, one skilled in the art would recognize from the disclosure that the applicant was in possession of the genus of DNAs that comprise SEQ ID NO: 2.

**Conclusion:** The written description requirement is satisfied.

**Example 9: Hybridization**

**Specification:** The specification discloses a single cDNA ( SEQ ID NO:1) which encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity. The specification includes an example wherein the complement of SEQ ID NO: 1 was used under highly stringent hybridization conditions (6XSSC and 65 degrees Celsius) for the isolation of nucleic acids that encode proteins that bind to dopamine receptor and stimulate adenylate cyclase activity. The hybridizing nucleic acids were not sequenced. They were expressed and several were shown to encode proteins that bind to a dopamine receptor and stimulate adenylate cyclase activity. These sequences may or may not be the same as SEQ ID NO: 1.

**Claim:**

An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1,

wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.

**Analysis:**

A review of the full content of the specification indicates that the essential feature of the claimed invention is the isolated nucleic acid that hybridizes to SEQ ID NO: 1 under highly stringent conditions and encodes a protein with a specific function. The art indicates that hybridization techniques using a known DNA as a probe under highly stringent conditions were conventional in the art at the time of filing.

The claim is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO: 1 and must encode a protein with a specific activity.

The search of the prior art indicates that SEQ ID NO: 1 is novel and unobvious.

There is a single species disclosed (a molecule consisting of SEQ ID NO: 1) that is within the scope of the claimed genus.

There is actual reduction to practice of the disclosed species.

Now turning to the genus analysis, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of

skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

**Conclusion:** The claimed invention is adequately described.

**Example 10: Process claim**

**Specification:** The specification teaches that SEQ ID NO: 10 is an EST. The specification also teaches that SEQ ID NO: 10 is a chromosome marker and that any DNA which hybridizes under specified stringent conditions to SEQ ID NO: 10 will be useful as a marker for detecting the presence of Burkitt's lymphoma. The specification also teaches how to produce DNAs including genomic DNAs which hybridize to SEQ ID NO: 10 and isolation of said DNAs. The specification presents an example where a genomic DNA is probed with SEQ ID NO: 10 under the specified stringent conditions (6XSSC and 65 degrees Celsius) and the genomic DNA which hybridizes under these conditions is isolated and is sequenced. The sequence of this genomic clone is represented by SEQ ID NO: 11.

**Claim:**

Claim 1: A process for producing an isolated polynucleotide comprising hybridizing SEQ ID NO: 10 to genomic DNA in 6XSSC and 65° C and isolating the DNA polynucleotide detected with SEQ ID NO: 10.

Claim 2: An isolated DNA that hybridizes with SEQ ID NO: 10.

**Analysis:**

**Claim 1:**

A review of the full content of the specification indicates that the essential feature of the claimed invention is a process of obtaining a nucleic acid sequence which is identified by a probe that hybridizes to SEQ ID NO:10 and a polynucleotide that hybridizes with SEQ ID NO: 10. The

specification and the general state of the art indicate that the general process of producing nucleic acids through hybridization with probes was routine at the time of filing.

The claim is drawn to a genus i.e., a process of hybridizing to genomic DNA with SEQ ID NO: 10 and isolating the DNA which hybridizes under specific conditions to said sequence.

The search indicates that SEQ ID NO: 10 and SEQ ID NO: 11 are novel and unobvious sequences. Therefore, under the examination guidelines of *In re Ochiai* and *In re Brouwer*, the method of making a novel and unobvious product is also novel and unobvious.

The specification presents an example where a single species has been reduced to practice, i.e., isolation of SEQ ID NO: 11 based on hybridization with SEQ ID NO: 10. Therefore the disclosed species within the genus has been adequately described. Now turning to the genus analysis, the art indicates that there is no substantial variation within the genus because of the stringency of hybridization conditions which yields structurally similar molecules. The single disclosed species is representative of the genus because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus.

**Claim 2:**

The claim is drawn to a genus of nucleic acids, all of which must hybridize to SEQ ID NO: 10. The claim does not specify any stringency conditions. The claim is broad and reads on virtually any nucleic acid.

There is a species disclosed, SEQ ID NO: 11. The art indicates that there is substantial variation within the genus because the lack of stringency of hybridization conditions would be expected to yield structurally unrelated nucleic acid molecules. The single disclosed species is not representative of the genus because there is no structural attribute or feature that is common to the members of the genus.

**Conclusion:**

Claim 1 is adequately described.

Claim 2 should be rejected as lacking adequate written description following the analysis described above.

**Note: Applicant may overcome the written description rejection of the product by, for example, substituting claim 2 with a product by process claim such as the one below.**

Claim 2. *The isolated DNA polynucleotide prepared according to the process of claim 1.*

**Example 11: Allelic Variants**

**Specification:** The specification discloses a DNA, SEQ ID NO: 1, said to encode a cell surface receptor for adenovirus. The cell surface receptor is designated protein X and its sequence is given as SEQ ID NO:2. The specification states that the invention includes alleles of the DNA that include single nucleotide polymorphisms (SNPs). No allelic sequence information is disclosed, but the specification states that allelic variants of SEQ ID NO: 1 can be obtained, e.g., by hybridizing SEQ ID NO: 1 to a DNA library made from the species of organism that yielded SEQ ID NO: 1.

**Claims:**

1. An isolated DNA that encodes protein X (SEQ ID NO: 2).

2. An isolated allele of the DNA according to claim 1, which allele encodes protein X (SEQ ID NO: 2).

3. An isolated allele of SEQ ID NO: 1.

**Analysis:**

**Claim 1:**

Claim 1 is drawn to the genus of DNAs that encode amino acid sequence SEQ ID NO:2, i.e., all sequences degenerately related by a genetic code table to SEQ ID NO:1. Although only one specie within the genus is disclosed, SEQ ID NO:1, a person of skill in the art could readily envision all the DNAs degenerate to SEQ ID NO:1 by using a genetic code table. One of skill in the art would conclude that applicant was in possession of the

genus based on the specification and the general knowledge in the art concerning a genetic coding table.

**Claim 2:**

Claim 2 is drawn to a subgenus of allelic DNAs that encode amino acid sequence SEQ ID NO: 2. The specification does not provide any particular definition for the term allele. In this circumstance, the meaning of the term is the ordinary usage in the art. The ordinary meaning of the term allele is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutational sites. See, Rieger et al., *Glossary of Genetics* (1991), p. 16. The alleles in claim 2 are "strictly neutral" because they encode identical proteins, and make no difference to phenotype. See, Rieger et al., p. 17. Although the standard definition refers to genomic sequences and the claims are directed to DNAs, a reasonable interpretation is that the claim is directed to DNAs that include naturally occurring mutational site(s).

The specification discloses only one allele within the scope of the genus: SEQ ID NO:1. The specification proposes to discover other members of the genus by using a hybridization procedure. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO: 1 relates to the structure of any strictly neutral alleles. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is that they are variant structures, and in the present state of the art the structure of one does

not provide guidance to the structure of others. The common attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

**Claim 3:**

Claim 3 is drawn to the genus including all DNA alleles of SEQ ID NO: 1. The specification does not provide any particular definition for the term allele. In this circumstance, the meaning of the term is the ordinary usage in the art. The ordinary meaning of the term allele is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutational sites. See, Rieger et al., *Glossary of Genetics* (1991), p. 16. The Rieger reference discloses that there are at least seven different kinds of allele in addition to the "strictly neutral" type discussed above for Claim 2. See, Rieger, pp. 16-17 (amorphs, hypomorphs, hypermorphs, antimorphs, neomorphs, isoalleles, and unstable alleles). The alleles are distinguished by the effect their different structures have on phenotype. According to Rieger, alleles may differ functionally according to their distinct structures. For example, they may differ in the amount of biological activity the protein product may have, may differ in the amount of protein produced, and may even differ in the kind of activity the protein product will have.

The specification discloses only one allele within the scope of the genus: SEQ ID NO:1. The specification proposes to discover other

members of the genus by using a hybridization procedure. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO: 1 relates to the structure of different alleles. In addition, according to the standard definition, the genus includes members that would be expected to have widely divergent functional properties. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of other unknown alleles having concordant or discordant functions. The common attributes of the genus are not described and the identifying attributes of individual alleles, other than SEQ ID NO:1, are not described. The nature of alleles is that they are variant structures where the structure and function of one does not provide guidance to the structure and function of others. According to these facts, one of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

**Conclusions:**

**Claim 1:**

Claim 1 should not be rejected under the written description requirement.

**Claim 2:**

Claim 2 should be rejected under the written description requirement. An analysis similar to the one set forth above could be used. Since the Office has the burden of presenting evidence to support its position, see

MPEP 2163.04, a reference should be relied on as authority for the Office's interpretation of the claim term "allele."

**Claim 3:**

Claim 3 should be rejected under the written description requirement. An analysis similar to the one set forth above could be used. Since the Office has the burden of presenting evidence to support its position, see MPEP 2163.04, a reference should be relied on as authority for the Office's interpretation of the claim term "allele."

For the rejections of claims 2 and 3, the Office interpretation of "allele" should be supported by a reference, rather than by taking "notice," because the interpretation is the principle evidence supporting the rejection. See MPEP 2144.03 (For further views on official notice, see *In re Ahlert*, 424 F.2d 1088, 1091 165 USPQ 418, 420 - 421 (CCPA 1970) ("[A]ssertions of technical facts in areas of esoteric technology must always be supported by citation of some reference work" and "allegations concerning specific `knowledge' of the prior art, which might be peculiar to a particular art should also be supported." Furthermore the applicant must be given the opportunity to challenge the correctness of such assertions and allegations. "The facts so noticed serve to `fill the gaps' which might exist in the evidentiary showing" and should not comprise the principle evidence upon which a rejection is based.); see also, *In re Barr*, 444 F.2d 588, 170 USPQ 330 (CCPA 1971) (scientific journal references were not used as a basis for taking judicial notice that controverted phrases were art - recognized because the court was not sure that the meaning of the term at issue was indisputable among reasonable men); *In re Eynde*, 480 F.2d 470, 178 USPQ

470,474 (CCPA 1973) ("The facts constituting the state of the art are normally subject to the possibility of rational disagreement among reasonable men and are not amenable to the taking of [judicial] notice.").)

**Example 12: Bioinformatics**

**Specification:** The specification discloses a process for identifying and selecting biological compounds that are present in a biological system in a tissue specific manner. In the disclosed process the expression level of a set of compounds is quantitatively determined in multiple tissues within an organism. The expression level data is then graphically displayed in such a manner that compounds that are differentially expressed are easily identified. An artisan interested in identifying a compound that is expressed at a high level in one tissue and at a different level in a second tissue may easily select compounds that are expressed in a tissue specific manner based on the displayed information. The specification indicates that the compounds to be detected encompass DNA, RNA and proteins as well as metabolites. The specification does not provide any particular examples, but discloses that the expression levels can be determined by any analytical method consistent with the class of compounds being detected. This type of measurement requires actual physical steps.

**Claim:**

A computer-implemented method of selecting tissue specific compounds, said method comprising the steps of:

(a) analyzing the expression level of compounds in a first and second tissue and obtaining expression level data for each of said compounds;

(b) inputting the expression level data obtained in step a) into a computer;

(c) displaying a first axis corresponding to the expression level of each of said compounds in said first tissue;

(d) displaying a second axis substantially perpendicular to said first axis, said second axis corresponding to the expression level data of each of said compound in said second sample

(e) displaying a mark at a position, wherein said position is selected relative to said first axis in accordance with an expression level of each of said compound in said first sample and relative to said second axis in accordance with the expression of said compound in said second sample; and

(f) selecting a compound of interest based on the position of the mark.

**Analysis:**

A review of the full content of the specification indicates that obtaining, inputting, and displaying the expression level of compounds is essential to the operation of the claimed invention.

A search of the prior art indicates that obtaining the expression level data of compounds is conventional in the art, and that data display devices and associated support algorithms are well known in the art.

A review of the claim indicates that the claim is drawn to a generic environment for the display of compounds in a tissue specific manner.

Since there is no species claimed or disclosed, the claim is analyzed as a claim drawn to a single embodiment. There is no actual reduction to practice of the claimed invention, or clear depiction of the claimed invention

in detailed drawings. However, reading the specification in light of the knowledge and level of skill in the art, the specification discloses the complete steps of the claimed process. See In re Hayes Microcomputer Products Inc. Patent Litigation, 982 F2d. 1527, 1534-35, 25 USPQ2d 1241, 1246 (Fed. Cir. 1992), where the court stated,

> One skilled in the art would know how to program a microprocessor to perform the necessary steps desired in the specification. Thus, an inventor is not required to describe every detail of his invention. An applicant's disclosure obligation varies according to the art to which the invention pertains.

In this fact situation, the art is sufficiently developed so as to put one of skill in the art in possession of the complete steps of the process. In other words, one skilled in the relevant art would understand what is intended by the claimed invention and know how to carry it out.

**Conclusion:** There is adequate written description for what is claimed.

**Example 13: Protein Variant**

**Specification:** The specification describes a protein isolated from liver. A working example shows that the isolated protein was sequenced and determined to consist of SEQ ID NO: 3. The isolated protein was additionally characterized as being 65 kD in molecular weight and having tumor necrosis activity. The specification states that the invention provides variants of SEQ ID NO: 3 having one or more amino acid substitutions, deletions, insertions and/or additions. No further description of the variants is provided. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and/or additions are routine in the art. The specification does not define when a protein ceases to be a variant of SEQ ID NO: 3.

**Claims:**

1. An isolated protein having SEQ ID NO: 3.

2. An isolated variant of the protein of claim 1.

**Analysis:**

**Claim 1**:

A search of the prior art indicates that SEQ ID NO: 3 is novel and nonobvious. The claim is directed to a genus of proteins that comprise SEQ ID NO: 3. One member of the genus, SEQ ID NO: 3, is described by a complete structure.

There is relatively little variation among the species within the genus because each member of the genus shares SEQ ID NO: 3 as a necessary common feature. The single disclosed example is representative of the claimed genus because taken in view of the general knowledge in the art, the disclosure is sufficient to show that one of skill in the art would conclude that applicant was in possession of the claimed genus.

**Claim 2:**

This is a genus claim. According to the specification, the term variant means a protein having one or more amino acid substitutions, deletions, insertions and/or additions made to SEQ ID NO: 3. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO: 3. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these types of changes are routinely done in the art, the specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 3 alone is insufficient to

describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

**Conclusions:**

**Claim 1:**

The claimed subject matter is adequately described. A rejection under the written description requirement should not be entered.

**Claim 2:**

The claimed subject matter is not supported by an adequate written description because a representative number of species have not been described. A rejection under the written description requirement, relying on the analysis set out above, should be entered.

**Example 14: Product by Function**

**Specification:** The specification exemplifies a protein isolated from liver that catalyzes the reaction of A $\longrightarrow$ B. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

**Claim:**

A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A $\longrightarrow$ B.

**Analysis:**

A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.

A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3. Additionally, the claim is drawn to a protein which **comprises** SEQ ID NO: 3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising".

The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.

A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.

There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that

applicant was in possession of the necessary common attributes possessed by the members of the genus.

**Conclusion:** The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.

**Example 15: Antisense**

**Specification:** The specification discloses a messenger RNA sequence, SEQ ID NO: 1, which encodes human growth hormone. The specification states that the invention includes antisense molecules that inhibit the production of human growth hormone. The specification describes an art-recognized method of screening for antisense molecules that is called "gene walking." Gene walking is said to involve obtaining antisense oligonucleotides that are complementary to the target sequence.

**Claim:**

An antisense oligonucleotide complementary to a messenger RNA having SEQ ID NO: 1 and encoding human growth hormone, wherein said oligonucleotide inhibits the production of human growth hormone.

**Analysis:**

A review of the full content of the specification indicates that the complement of SEQ ID NO: 1 is essential to the operation of the claimed invention. The general knowledge in the art is that any full-length complement of a target mRNA inhibits the function of the mRNA and is therefore an antisense oligonucleotide. Thus, one of skill in the art would view applicant's disclosure of a coding sequence, with the statement that the invention includes antisense oligonucleotides, as an implicit disclosure that the full-length complement of SEQ ID NO: 1 is an antisense oligonucleotide.

It is generally accepted in the art that oligonucleotides complementary to a messenger RNA, including fragments of the full-length complement, have antisense activity when they match accessible regions on the target mRNA. Generally, the closer the complementary fragment is to full length, the greater the likelihood it will have antisense activity. In addition, oligos that retain complementarity to the Shine-Delgarno sequence usually have antisense activity.

The claim is drawn to the genus of antisense molecules that inhibit the production of human growth hormone encoded by SEQ ID NO: 1. There is a single species described with a complete structure, i.e., the full-length complement of SEQ ID NO: 1. In addition to the full-length complement, the genus includes fragments of the complement that retain antisense activity.

The procedures for making oligonucleotide fragments of the SEQ ID NO: 1 complement are conventional, e.g., any specified fragment can be ordered from a commercial synthesizing service. The procedures for screening for antisense activity are also conventional, and the specification describes the assay needed to do gene walking. The experience accumulated in the art with gene walking is that numerous regions of a target are accessible, that these regions are identified routinely, and that antisense oligonucleotides are complementary to these accessible regions. The full-length complement and longer fragments match multiple accessible regions; shorter fragments match fewer accessible regions.

When considering the distinguishing characteristics of the claimed invention, the sequence provided in the specification defines and limits the

structure of any effective antisense molecules. The specification also teaches the functional characteristics of the claimed invention as well as a routine art recognized method of making and screening for the claimed invention. Considering the specification's disclosure of:

(1) the sequence (SEQ ID NO: 1) which defines and limits the structure of any effective antisense molecules such that one skilled in the art would be able to immediately envisage members of the genus embraced by the claim, and

(2) the functional characteristics of the claimed invention as well as a routine art-recognized method of screening for antisense molecules which provide further distinguishing characteristics of the claimed invention, along with

(3) the general level of knowledge and skill in the art,

one skilled in the art would conclude that applicant was in possession of the invention.

**Conclusion:** The claimed invention is adequately described.

**Example 16: Antibodies**

**Specification:** The specification teaches that antigen X has been isolated and is useful for detection of HIV infections. The specification teaches antigen X as purified by gel filtration and provides characterization of the antigen as having a molecular weight of 55 KD. The specification also provides a clear protocol by which antigen X was isolated. The specification contemplates but does not teach in an example antibodies which specifically bind to antigen X and asserts that these antibodies can be used in immunoassays to detect HIV. The general knowledge in the art is such that antibodies are structurally well characterized. It is well known that all mammals produce antibodies and they exist in five isotypes, IgM, IgG, IgD, IgA and IgE. Antibodies contain an effector portion which is the constant region and a variable region that contains the antigen binding sites in the form of complementarity determining regions and the framework regions. The sequences of constant regions as well as the variable regions subgroups (framework regions) from a variety of species are known and published in the art. It is also well known that antibodies can be made against virtually any protein.

**Claim:** An isolated antibody capable of binding to antigen X.

**Analysis:**

A review of the full content of the specification indicates that antibodies which bind to antigen X are essential to the operation of the claimed invention. The level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-

characterized antigen was conventional. This is a mature technology where the level of skill is high and advanced.

The claim is directed to any antibody which is capable of binding to antigen X.

A search of the prior art indicates that antigen X is novel and unobvious.

Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X.

**Conclusion:** The disclosure meets the requirement under 35 USC 112 first paragraph as providing an adequate written description of the claimed invention.

**Example 17: Genus-species with widely varying species**

**Specification:** The specification discloses the rat cDNA sequences for proinsulin and pre-proinsulin and a method for determining the corresponding human and other mammalian insulin cDNA sequences. However, the specification does not disclose any actual cDNA sequence other than the rat proinsulin and pre-proinsulin sequence. The specification discloses that one human proinsulin amino acid (but not cDNA) sequence was known at the time of filing. The art recognized that the sequence of human insulin proteins, and therefore also cDNAs, would probably vary among individuals. The specification also discloses that pre-proinsulin is post translationally modified to form proinsulin, and that proinsulin is cleaved to form insulin.

**Claims:**

Claim 1. An isolated mammalian cDNA encoding insulin.

Claim 2. The isolated cDNA of claim 1 wherein the mammalian cDNA is human.

**Analysis:** The examiner should analyze claim 2 first because it is drawn to a subgenus of the genus of claim 1.

**Claim 2:**

A review of the full content of the specification indicates that human cDNA molecules that encode insulin are essential to the operation/function of the invention.

Claim 2 is directed to a genus of human cDNA which encodes insulin.

There is no species of human insulin cDNA disclosed.

Based upon art published after applicant's filing date there is expected to be variation among the species of cDNA which encode human insulin because the sequence of human insulin proteins, and therefore also human insulin cDNAs, would be expected to vary among individuals.

The specification discloses only the sequence of a single human proinsulin protein, and does not disclose any human cDNA sequence at all.

In addition, there is no evidence on the record of a relationship between the structure of rat insulin cDNA and the structure of insulin cDNAs from humans or other mammals that would provide any reliable information about the structure of other insulin cDNAs on the basis of the rat insulin cDNA.

There is no evidence on the record that the disclosed rat cDNA proinsulin sequence had a known structural relationship to the human cDNA sequence, or to other mammalian cDNA sequences; the specification discloses only a single human proinsulin (protein) sequence; the art indicated that human proinsulin proteins were expected to be variable in structure; and there is expected to be variation among human cDNAs that

encode a given human proinsulin. In view of the these considerations, a person of skill in the art would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed human cDNA.

**Claim 1:**

Claim 1 is directed to a genus of mammalian cDNAs which encode insulin. The specification evidences actual reduction to practice of the rat cDNA sequences for proinsulin and preproinsulin, but does not disclose any other cDNA sequences. The art indicates that there is likely to be substantial variation among the species within the genus of cDNAs that encode mammalian insulins because the sequences of the mammalian insulin proteins, and therefore the mammalian cDNAs, would be expected to vary among species.

The specification discloses a method for determining the corresponding human and other mammalian insulin cDNA sequences as well as the function of the claimed sequences. However, neither the specification nor the general knowledge of those skilled in the art provide evidence of any partial structure which would be expected to be common to the members of the genus. Moreover, there is post filing date evidence that indicates that there is a lack of a structural relationship between the rat insulin cDNA sequences and other mammalian insulin cDNA sequences. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by members of the genus, because rat cDNA sequences are not representative of the claimed genus. Consequently, since applicant was in

possession only of the rat insulin cDNA and since the art recognized variation among the species of the genus of cDNAs that encode mammalian insulin, the rat insulin cDNA was not representative of the claimed genus. Therefore, the applicant was not in possession of the genus of mammalian insulin cDNAs as encompassed by claim 1.

**Conclusion:**

Claims 1 and 2 do not meet the written description requirement.

**Example 18: <u>Process claim where the novelty is in the method steps.</u>**

**Specification:** The specification teaches a method for producing proteins using mitochondria from the fungus *Neurospora crassa*. In the method, mitochondria are isolated from this fungus and transformed with a mitochondrial expression vector which comprises a nucleic acid encoding a protein of interest. The protein is subsequently expressed, the mitochondria is lysed, and the protein is isolated. The specification exemplifies the expression of β-galactosidase using the claimed method using a cytochrome oxidase promoter.

**Claim:**

1. A method of producing a protein of interest comprising;

obtaining *Neurospora crassa* mitochondria,

transforming said mitochondria with a expression vector comprising a nucleic acid that encodes said protein of interest,

expressing said protein in said mitochondria, and

recovering said protein of interest.

**Analysis:**

A review of the specification reveals that *Neurospora crassa* mitochondrial gene expression is essential to the function/operation of the claimed invention. A particular nucleic acid is not essential to the claimed invention.

A search of the prior art reveals that the claimed method of expression in *Neurospora crassa* is novel and unobvious.

The claim is drawn to a genus, i.e., any of a variety of methods that can be used for expressing protein in the mitochondria.

There is actual reduction to practice of a single embodiment, i.e., the expression of β-galactosidase.

The art indicates that there is no substantial variation within the genus because there are a limited number of ways to practice the process steps of the claimed invention.

The single embodiment is representative of the genus based on the disclosure of *Neurospora crassa* mitochondria as a gene expression system, considered along with the level of skill and knowledge in the gene expression art. One of skill in the art would recognize that applicant was in possession of all of the various expression methods necessary to practice the claimed invention.

**Conclusion:**

The claimed invention is adequately described.